ULTRASONOGRAPHIC ANALYSIS OF SALIVARY GLANDS AND BIOCHEMICAL ANALYSIS OF WHOLE SALIVA IN PRE AND POST RADIOTHERAPY ORAL CANCER PATIENTS

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CONTENTS

LIST OF ABBREVIATIONS USED

USG	Ultrasonography
PG	Parotid
SM	Submandibular
RT	Radiotherapy
RT parotid	Right parotid
LT parotid	Left parotid
RT submandibular	Right submandibular
LT submandibular	Left submandibular
Stage I	Pre radiotherapy
Stage II	Post radiotherapy
Na	Sodium
K	Pottasium
Ca	Calcium

LIST OF PHOTOGRAPHS

S.NO	PHOTOGRAPHS
1	Armamentarium
2	Usg machine
3	Centrifugal apparatus
4	Easy lyte na/k analyser
5	Erba 640
6	Erba kit
7	Calcium kit
8	Ph strip
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ABSTRACT

BACKGROUND:

Oral squamous cell carcinoma(OSCC) is the sixth most common human cancer, with an increasing incidence in younger people causing a high morbidity &mortality rate in older persons. The mainstay of treatment for OSCC is usually surgery followed by radiotherapy. One of the important complication of Radiotherapy is its potential to damage the major salivary glands. It causes morphological alterations in the glands and also affects the composition of saliva.

AIM:

To analyse ultrasonographic changes of parotid and submandibular salivary glands and Biochemical analysis of whole saliva in oral cancer patients before and after radiotherapy

OBJECTIVES:

Ultrasonographic analysis of parotid &submandibular salivary glands size , margins, echotexture, echogenicity,and vascularity(colour Doppler) before and six weeks after radiotherapy and Assessment of salivary Na, K, Ca, pH, salivary amylase , salivary total protein in oral cancer patients before and six weeks after radiotherapy.

METHODS:

A total of 30 oral cancer patients were selected for this study. Among the 30 patients 23 were males and 7 females. Age range of the patient was 30-70. All were planned for conventional radiation treatment.

Ultrasonographic evaluation of 60 parotids and 60 submandibular glands were done prior to radiotherapy and six weeks after completion of radiotherapy. Unstimulated Whole saliva was collected under resting conditions in a quiet room, between 8 am and noon, at least 1 hour after food intake in same patients on the day of ultrasound.

RESULTS:

When comparing the post radiotherapy USG changes of salivary glands length, width, depth with preradiotherapy USG values, and the salivary salivary biochemical pre and post radiotherapy values, we found that the results were statistically significant. P value =0.000.

CONCLUSION:

On ultrasonographic examination we observed decrease in size of salivary glands following radiotherapy. There was significant decrease in length, width and depth and changes in margin from regular to irregular, echotexture from homogenous to heterogenous and echogenicity from hyperechoic to hypoechoic. This changes salivary glands can be related to chronic inflammation which sets in the glands after exposure to radiation and which leads to subsequent fibrous changes in glands. In salivary evaluation pH is significantly reduced, Na, Ca, Total protein levels were significantly increased. Pottasium and salivary amylase levels were significantly reduced after radiotherapy. These changes can be related to parenchymal damage and acinar loss.

KEY WORDS:

Oral cancer, Radiotherapy, Ultrasonography, Salivary glands

INTRODUCTION

Oral cancer is a broad term that includes various malignant diagnoses that present in the oral tissues. Oral squamous cell carcinoma (OSCC) is the sixth most common human cancer, with an increasing incidence in younger people causing a high morbidity &mortality rate in older persons. Even though the management and prognosis may be different between types and stages of oral cancer, It always has a dramatic impact on the patient's life. Although the older literature combines oral cancer and oropharyngeal cancer, now a days it is recognized that both cancers should be evaluated individually for the ease of assessment of epidemiology, pathogenesis and treatment outcomes. The oral cavity includes the lips, the labial and buccal mucosa, the anterior two-thirds of the tongue, the retromolar pad, the floor of the mouth, the gingival, the hard palate. Oro pharynx includes the palatine and lingual tonsils, the posterior one-third of the tongue, the soft palate, and posterior pharyngeal wall.[1]

In South Asia, oral cancer accounts for about up to 40% of all cancers. In India, the incidence of oral cancer is about 3–7 times more common as compared with the resource-rich countries. Oral cancer is the 3rd most common cancer in India after cervical and breast cancer among women. The increased prevalence of the oral cancer in the subcontinent of India seems to be due to smoking, use of smokeless tobacco, alcohol, spicy food and lack of fruit or fiber intake, and neglected oral health and hygiene.

In the West, the cancers in the floor of mouth and tongue are common whereas in the Indian subcontinent the cancers of gingivobuccal sulcus, tongue, buccal mucosa are common due to placement of tobacco quid under the tongue, under the buccal mucosa and under the lip. Tobacco and alcohol are strong synergistic effects or oral cancer. There are strong synergistic

effects on oral cancer risk when a person has both the habit of smoking & drinking, tobacco usage including smokeless tobacco and excessive intake of alcohol which is estimated to account for about 90% of oral cancers.[2]

The mainstay of treatment for OSCC is usually surgery[3] followed by radiotherapy [external beam radiotherapy (EBRT) and/or brachytherapy], or various combinations of these modalities with or without the use of systemic therapy like chemotherapy and/or target agents. The basis of treatment selection depends on considerations of disease control, anticipated functional and cosmetic outcomes, and availability of resources and expertise. OSCCs are considered radiosensitive and early lesions are highly curable mainly T_1 and T_2 lesions.

One of the important complication of Radiotherapy is its potential to damage the major salivary glands. There are three pairs of major salivary glands in human body namely parotid glands, submandibular glands and sublingual glands. Moreover, numerous minor salivary glands are also found in the oral cavity

Parotid glands contributes the majority of stimulated saliva and submandibular glands contribute approximately 2/3rds of un stimulated saliva volume.[4] Saliva is the product of multiple salivary glands both major and minor. Salivary gland plays an important role in oral health by aiding in digestion of food, protection of oral mucosa, it also facilitates remineraliation of dental hard tissues and moisturizing palate for articulation. Each gland has a unique combination of mucous and serous acinar cells which are responsible for synthesizing protein componants of saliva and transporting water and electrolytes.

The complications of Radiotherapy is due to effects on vascular, connective and parenchymal tissues.

The radiation uptake by salivary glands during radiotherapy for oral cancers alters the parenchymal structure and vascularity resulting viscosity and volume changes of secreted saliva.[5] Due to the functionl and structural alterations of the salivary glands, biochemical alterations of saliva also occurs. Despite their slow turnover rate, the serous cells are highly radiosensitive. In submandibular glands, the selective destruction of serous acini was particularly apparent within the normal mix of cells. Although acinar cells can recover and repopulate, the typical therapeutic radiation doses eventually damage the ducts, ductal stem cells, and the mucinous and supporting stromal and vascular cells. This damage often result in xerostomia and fibrosis. A radiation dose as low as 20 Gy can cause permanent cessation of salivary flow if given as a single dose. At doses above 52Gy, salivary dysfunction becomes severe. Treatment of oral carcinoma traditionally involves the administration of a dose of 60Gy to 70Gy and this can lead to a rapid decrease in flow during the first week of radiation, with an eventual reduction of 95% in the region. By 5 weeks of radiation, the flow virtually ceases and rarely recovers completely. Both resting and stimulated salivary flow are inhibited.

Various imaging modalities were used to evaluate the radiation induced salivary gland changes which includes CT scan,MRI and sonography. Ultrasonography is a simple and safe technique for the evaluation of salivary gland changes caused by radiotherapy.[6]

Ultrasonographic(USG) imaging is considered as a “real-time” imaging, which generate electrical impulses that are converted into sound waves of high frequency by a transducer and then transmitted into the tissues to be examined. It is then reflected as echoes

and reconverted into electrical energy, amplified, processed, and displayed on the monitor.[7] USG is particularly suitable for imaging superficial structures of the oral mucosa and provides both quantitative and qualitative assessment, the nature and dimension of lesion or structure.[8]

Based on this the study is planned to evaluate the changes in Parotid and Submandibular salivary glands in patients with oral cancer undergoing radiotherapy treatment using Ultrasonography and biochemical analysis(Na, K, Ca, PH, amylase, Total protein) of their saliva at the same time.

AIM AND OBJECTIVES

AIM:

To analyse ultrasonographic changes of parotid and submandibular salivary glands and Biochemical analysis of whole saliva in oral cancer patients before and after radiotherapy.

OBJECTIVES:

1. Ultrasonographic analysis of parotid &submandibular salivary glands size ,margins, Echotexture, Echogenicity,and vascularity (colour Doppler) before radiotherapy.
2. Assessment of salivary Na, K, Ca, pH, salivary amylase, salivary total protein in oral cancer patients before radiotherapy.
3. Ultrasonographic analysis of parotid & submandibular salivary glands size, margins, Echotexture, Echogenicity, and vascularity(colour Doppler) six weeks after completion of radiotherapy.
4. Assessment of salivary Na, K, Ca, pH, salivary amylase, salivary total protein in oral cancer patients six weeks after completion of radiotherapy.
5. To compare the pre radiotherapy Ultrasonographic analysis of parotid and submandibular gland with post radiotherapy ultrasonographic changes.
6. To compare the pre radiotherapy biochemical values of saliva with post radiotherapy values.
7. To find association between TNM staging of tumour with pre and post radiotherapy Ultrasonographic salivary gland changes.

REVIEW OF LITERATURE

Our oldest description of cancer (although the word cancer was not used) was discovered in Egypt and dates back to about 3000 BC. It's called the Edwin Smith Papyrus and is a copy of part of an ancient Egyptian textbook on trauma surgery.

The origin of the word cancer is credited to the Greek physician Hippocrates (460-370 BC), who is considered the "Father of Medicine." Hippocrates used the terms carcinos and carcinoma to describe non-ulcer forming and ulcer-forming tumors. In Greek, these words refer to a crab, most likely applied to the disease because the finger-like spreading projections from a cancer called to mind the shape of a crab.[9]

Head and neck malignancies comprise 3–5% of all malignancies in worldwide.[2]In epidemiology studies the term 'oral cancer' is sometimes employed to connote both oral cavity cancer and oropharyngeal cancer. However, these are different clinical entities and in contemporary practice often have different etiologies and are frequently managed differently according to American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) in the tumor-node-metastasis (TNM) staging classification squamous cell carcinomas of the oral cavity (OSCC) originating from the mucosal lip, anterior two-thirds of the tongue (oral tongue), buccal mucosa, floor of mouth, hard palate, lower and upper alveolus and gingiva, and the retromolar trigone.[3]

The mainstay of treatment for OSCC is usually surgery.[10] EBRT with or without chemotherapy is generally employed in 3 situations: a) adjuvant to primary surgery to enhance loco-regional control (LRC) for cases with unfavorable pathological features, b) primary treatment for cases unable to tolerate or unsuited for surgery, and c) salvage treatment in the persistent or recurrent disease setting. Brachytherapy may be employed as a sole modality for

early disease with a well-defined primary tumor, or as an adjuvant to surgery for cases with close or positive resection margins. Alternatively it may be used as a “boost” technique to the primary tumor in addition to EBRT.[1]

Evolution of radiotherapy

Radiation therapy is shaped by the efforts of many scientists in medicine, biology, physics as well as people in allied professions such as administration, computer science and architecture.

The radiotherapy era was divided into six periods, each 20 years long.

1. Discovery phase: :1898-1910
2. Empirical radiotherapy phase :1910-1930
3. Scientific radiotherapy phase :1930-1950
4. Transition to megavoltage phase :1950-1970
5. Modernization phase (buildings & machines). :1970-1990
6. High technology phase : 1990- present

Rothwell states that most orofacial complications are dose dependent and that severe side effect occurs when doses <45 Gy administered be the bilaterally to the mouth, jaws, and salivary gland.[11]

PRINCIPLES OF RADIOTHERAPY

Effects of radiation at cellular level

The effectiveness of ionizing radiation on a biologic system depends not only on the amount of radiation deposited but also on the state of the biologic system. One of the first laws of radiation biology, postulated by Bergonie and Tribondeau, stated in essence that the radiosensitivity of a tissue is dependent on the number of undifferentiated cells in the tissue, the degree of mitotic activity of the tissue, and the length of time that cells of the tissue remain in active proliferation.[3]

The primary target of ionizing radiation is the DNA molecule, and the human cell is most radiosensitive during mitosis. Current research tends to indicate that all cells are equally radiosensitive; however, the manifestation of the radiation injury occurs at different time frames (i.e., acute versus late effects).

Because tissue cells are composed primarily of water, most of the ionization occurs with water molecules. These events are called indirect effects and result in the formation of free radicals such as OH, H^{+} and HO^{2-}. These highly reactive free radicals may recombine with no resultant biologic effect, or they may combine with other atoms and molecules to produce biochemical changes that may be deleterious to the cell. The possibility also exists that the radiation may interact with an organic molecule or atom, which may result in the inactivation of the cell; this reaction is called the direct effect. Because ionizing radiation is nonspecific (i.e., it interacts with normal cells as readily as with tumour cells), cellular damage will occur in both normal and abnormal tissue. The deleterious effects, however, are greater in

the tumour cells because a greater percentage of these cells are undergoing mitosis and tumour cells also tend to be more poorly differentiated. In addition, normal cells have a greater capability for repairing sublethal damage than do tumour cells. Thus greater cell damage occurs to tumour cells than to normal cells for any given increment of dose.

In terms of cellular lethality from ionizing radiation, DNA is generally considered to be a principal intracellular target. Although both single-strand breaks and **double-strand breaks (DSBs)** are observed, it is the double-strand breaks that are thought to represent the lethal event.

VARIOUS MODES OF RADIOTHERAPY

Three types of radiations are used: gamma, beta and X-rays. The radiation is concentrated onto the site of the tumour to damage the chromosomes in the rapidly-growing cancer cells.

Types of radiation therapy

1. External (transcutaneous): Irradiation from sources at a distance from the body (X-ray, teletherapy with radium – 226, cobalt – 60 or cesium – 137).

2. Local irradiation (brachytherapy): Irradiation from source in direct contact with the tumor:

a) Surface irradiation with applicators loaded with radioactive material (moulds for treatment for certain oral tumors like carcinoma of hard palate and skin tumor).

b) Intra cavitary irradiation with radio-active material (most commonly radium 226, cobalt-60 and cesium–137) in removable applicators which are inserted into body cavities, such as uterus, vagina nasopharynx or maxillary sinus.

c) Interstitial irradiation by removable needles containing radium – 226, cobalt – 60,cesium – 137; by non-removable "seeds" of radioactive gold – 198 or radon ; by small radioactive iridium sources in nylon suture ;or by radioactive tantalum – 182 wire. The radioisotope is implanted into the tumor, e.g. – carcinoma of tongue and buccal mucosa.

d) Direct Roentgen therapy to epithelial lesions by means of cones (i.e. – transvaginal, intraoral).

3. Intraoral or systematic irradiation: Eradiation by radioactive sources (i.e. - 32 p, 131 I) administered intravenously or parentally. Radioactive Iodine is used to treat thyroid cancer, and phosphorous – 32 is used for the treatment of polycythemia vera. Other methods like contact therapy, intraoperative, stereotactic hyperthermia are also practiced.

EXTERNAL BEAM TREATMENT

A beam of ionising radiation is aimed at the cancerous growth in this treatment. The source of the beam is moved around. In this way, the beam is always focused on the tumour, but doesn't take the same route through healthy tissue. The tumour gets a high dose, while the surrounding healthy tissue gets a lower dose. External radiotherapy uses X-rays and sometimes gamma rays. X-rays or gamma rays, which are both forms of electromagnetic radiation. Although they are produced in different ways, both use photons.

Low and medium energy X-rays are particularly suitable for treating cancers on the outside of the body. To reach internal tumors requires very high energy radiation is required. This can be produced by super high voltage machines but sometimes, a radioactive source such as cobalt-60 or iridium-137 is used. When they decay, these radioactive sources produce high energy X-rays and gamma rays. These radiations are more penetrating and are therefore

more suitable for internal tumors.

Gamma rays are produced when isotopes of certain elements release radiation energy when they break down. Each element breaks down at a specific rate and each gives off a different amount of energy, which affects how deeply it can penetrate into the body. Gamma rays produced by the breakdown of cobalt 60 are used in the treatment called the "gamma knife," The patient does not come into contact with any radioactive sources and does not become radioactive as a result of the treatment.

Cobalt machines were the mainstay of radiation oncology departments in the 1960s. These units, sometimes called "teletherapy units", consisted of a large machine with cobalt 60 housed in the head of the treatment unit. The unit although bulky, is diverse in its treatment scope, because patients can be treated in a rotational or fixed beam arrangement.

INTERSTITIAL AND INTRACAVITARY TREATMENT

Implant therapy (brachytherapy) is a method of radiation treatment using sealed radioactive sources placed at a short distances from the patient's tumor. These radioactive sources can be best described as interstitial or intracavitary. The interstitial method is the placement of a sealed radioactive source directly into the tumor, such as tongue. The intracavitary method is the placement of sealed radioactive source in a body cavity close to the tumor, such as the cervix.

These types of radiotherapy usually use a source of beta radiation like technetium-99. Beta radiation is short range so its effects are much localized. This means that a higher dose can be given with less damage to surrounding tissues. In both the instances, these radioactive sources can be permanent or removable. Sources come in different forms (eg. needles, tubes & seeds). Radioactive substitutes also vary and include cesium, strontium 89, phosphorous,

phosphate, or cobalt, gold, tantalum & indium.

Other methods of treatment

Contact therapy

It is the placement of radioactive sources directly on the tumor. In this therapy the source is usually embedded in a mold and left on and the tumor for a specified period.

INTRAOPERATIVE RADIATION THERAPY (IORT) & TOTAL BODY IRRADIATION (TBI)

These are two newer methods of treatment. IORT delivers the radiation dosage directly to the tumor during surgery. This technique is used in tumors that are deeply situated in the body where surrounding radiosensitive organs can be moved out of the treatment area. Therefore a larger single dose can be delivered directly to the tumor with the aim of destroying the tumor & any residual disease. It is a costly time consuming procedure because of the necessity of combining the operating room's sterile- technique situation with the high energy equipment in a shielded room needed for radiation protection, This technique is used in selected cases. In contrast, TBI focuses on irradiation of the entire body rather than a specific site. This technique is also used for only specific diseases. Patients preparing for bone marrow transplant are probably the most common candidates for TBI. Doses higher than those that cause death from bone marrow depletion can be given because bone marrow is replaced during the transplant.

Hyperthermia

This is another method of treatment. The basic principle is that the heat sometimes causes regression in tumors. A special unit is needed to perform the heating procedure on the patient. Then the patient is treated with conventional radiation therapy.

Stereotactic radiosurgery

This is a treatment technique that was introduced in the early 1950s. Stereotaxis (a method dealing with precise location in an area of the brain) is essential in this neurological procedure. The procedure does not involve actual surgery. The patient's head is placed in a special frame, which is attached to the patient' skull. The frame is used to aim high-dose radiation beams directly at the tumor inside the patient's head. The dose and area receiving the radiation are coordinated very precisely. Most nearby tissues are not damaged by this procedure. Stereotactic radiosurgery can be done in one of three ways. The most common technique uses a linear accelerator to administer high-energy photon radiation to the tumor. The gamma knife, the second most common technique, uses cobalt 60 to deliver radiation. The third technique uses heavy charged particle beams (such as protons and helium ions) to deliver stereotactic radiation to the tumor.

Stereotactic radiosurgery is mostly used in the treatment of small benign and malignant brain tumors including meningioma, acoustic neuroma, and pituitary cancer. It can also be used to treat other conditions like Parkinson's disease and epilepsy. Stereotactic radiosurgery can be used to treat metastatic brain tumors (cancer that has spread to the brain from another part of the body) either alone or along with whole-brain radiation therapy. Whole brain radiation therapy is a form of external radiation therapy that treats the centre brain with radiation.

Stereotactic radiotherapy uses essentially the same approach as stereotactic radiosurgery to deliver radiation to the target tissue. However, stereotactic radiotherapy uses multiple small tractions of radiation as opposed to one large dose. Giving multiple smaller doses may improve outcomes and minimize side effects. Stereotactic radiotherapy is used to

treat tumors in the brain as well as other parts of the body. Clinical trails are under way to study the effectiveness of stereotactic radiosurgery and stereotactic radiotherapy alone and in combination with other types of radiation therapy.

THREE –DIMENSIONAL (3-D) CONFORMAL RADIATION THERAPY

Traditionally, the planning of radiation treatments has been done in two dimensions (which and height). Three-dimensional (3-D) conformal radiation therapy uses computer technology to allow doctors to more precisely target a tumor with radiation beams (using width, height, and depth). Many radiation oncologists use this technique. A 3-D image of a tumor can be obtained using computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT). Using information from the image, special computer programs design radiation beams that "conform" to the shape of the tumor. Because the healthy tissue surrounding the tumor is largely spared by this technique; higher doses of radiation can be used to treat the cancer. Improved outcomes with 3-D conformal radiation therapy have been reported for nasopharyngeal, prostate, lung, liver, and brain cancers.

INTENSITY-MODULATED RADIATION THERAPY (IMRT)

IMRT is a new type of 3-D conformal radiation therapy that uses radiation beam (usually x-rays) of varying intensities to deliver different doses of radiation to small areas of tissue at the same time. The technology allows for the delivery of higher doses of radiation within the tumor and lower doses to nearby healthy tissue. Some techniques deliver a higher dose of radiation to the patient each day, potentially shortening the overall treatment time and improving the success of the treatment. IMRT may also lead to fewer side effects during

treatment.

The radiation is delivered by a linear accelerator that is equipped with a multileaf collimator (a collimator helps to shape or sculpt the beams of radiation). The equipment can be rotated around the patient so that radiation beams can be sent from the best angles. The beams conform as closely as possible to the shape of the tumor. Because IMRT equipment is highly specialized, not every radiation oncology center uses IMRT.

This new technology has been used to treat tumors in the brain, head and neck, nasopharynx, breast, liver, lung, prostate, and uterus. However, IMRT is not appropriate or necessary for every patient or tumor type. Long-term results following treatment with TMRT are becoming available.

Low –LET and high-LET radiation linear energy transfer (LET) describes the rate at which a type of radiation deposits energy as it passes through tissue. Higher levels of deposited energy cause more cells to be killed by a given dose of radiation therapy. Different types of radiation have different levels of LET. For example, x-rays, gamma rays and electrons are known as low-LET radiation. Neutrons, heavy ions, and pions are classified as high-LET radiation. Most high-LET radiation is investigational treatment. The cost of the equipment and the amount of specialized training needed to perform high-LET radiation therapy restrict its use to only a few facilities in the United States.

ANATOMY OF SALIVARY GLANDS

There are three pairs of major salivary glands in human body namely parotid glands, submandibular glands and sublingual glands. Moreover, numerous minor salivary glands are also found in the oral cavity.

Parotid gland:

Parotid gland is the largest salivary gland, which is located in the retromolar fossa. It is anterior to external auditory meatus, inferior to zygomatic arch, posterior and superior to angle of mandible and anteriorly overlaps with masseter muscle. It is composed of serous acinar cells, which produce serous saliva, mainly water in content. The imaginary phase formed by facial nerve divides the parotid gland into superficial and deep lobe.[12] The main salivary duct of parotid gland is stensen's duct which passes through buccinator muscle and enters the oral cavity through buccal mucosa at the upper second molar tooth level. Parotid gland mainly secretes saliva in stimulated conditions like chewing, and it secrets up to60% of saliva during mastication.[13]

Submandibular gland:

Submandibular glands is the second largest salivary gland, which is located under the floor of the oral cavity, anterior and inferior to parotid gland, posterior and inferior to mylohyoid muscle and superior to digastrics muscle.[12].submandibular gland consists of both serous and mucous acinar cells, which produce thicker and more viscous saliva. The main salivary duct of the submandibular duct is the whartons duct which passes through sublingual space and enters the oral cavity near the lingual frenula. Submandibular gland mainly secrets saliva in non – stimulated conditions and contributes up to 90% of total salivary output at the resting state. It secrets 20-40% of total saliva in stimulated conditions.[13]

Sublingual gland:

Sublingual gland is the smallest major salivary gland, which is located in the floor of the oral cavity, lateral to geniohyoid muscle, superior to mylohyoid muscle and medial to mandible similar to submandibular gland, sublingual gland also composed of both serous and mucous acinar cells, which reduce 2-5% of the total saliva upon stimulation.[12,13] the intra glandular ducts of sublingual glands may either drain in to wharton's duct or empty in to the floor of the oral cavity.

RADIATION INDUCED COMPLICATIONS

The oral complications of head and neck radiation can be divided into two groups on the basis of the usual time of their occurrence.

***ACUTE COMPLICATIONS** – A therapeutic dose of radiation in head and neck cancer usually comprises a total of 64 Gy to 70 Gy in 32–35 fractions with the daily dose of 1.8–2.0 Gy/fraction.

Acute complication appears 1–2 weeks after radiation starts, it depends on dose and site of radiation. It includes

Oropharyngeal mucositis(8)

Change in salivary composition

Alteration of taste (Dysguesia)

Infection (bacterial, fungal and viral)

CHRONIC COMPLICATION:

Trismus and fibrosis

Malnutrition

Osteo radionecrosis

Dental caries

Xerostomia

These symptoms can subside 2–4 weeks after completion of radiotherapy occasionally tissue necrosis can be seen late during therapy, but this is relatively rare.[14]

EFFECT OF RADIATION ON ORAL AND SALIVARY GLAND TISSUS:

Radiotherapy for head and neck tumours is a viable treatment modality. Radiotherapy is concerned with the delivery of the correct radiation dose to the tumour mass. While minimizing the dose received outside the tumour zone. Rothwell states that most orofacial complications are dose dependent and that severe side effects occur when doses greater than 45 Gy are administered bilaterally to the mouth, jaws and salivary glands. Radiotherapy for malignancies in the oropharyngeal region consist of 2 Gy delivered daily and bilaterally through 8 x 10 cm fields over the oropharynx for a weekly exposured to 10Gy. This is continued typically until a total of 50 Gy is admnistered

Oral Mucous Membrane

Oral mucosal response to irradiation, by a series of changes which are related to dose and duration of therapy. Fractionated doses, each of 2 Gy / day result in the development of mucosal erythema within one week. At doses up to 1.8 Gy five times weekly all killing are repopulation of mucous membrane stem cells are essentially in equilibrium.

Daily treatment doses greater than 2Gy and large treatment volumes result in cell killing exceeding the proliferative capacity. As a result almost all patients develop a confluent mucositis by the third week. The mucosal erythema is due to thinning of epithelium and vascular dilation, inflammation and oedema of the submucosa. With continued radiotherapy, the mucosa becomes denuded, ulcerated and covered with fibrinous exudates.[15]

Mucositis commonly persists for two – three weeks after completion of radiotherapy.

Taste buds:

Taste buds are sensitive to radiation. Patients often note loss of taste acuity during the 2^{nd} and 3^{rd} week of radiotherapy. Bitter and acid flavours are more severely affected when the posterior two thirds of the tongue is irradiated and salt and sweet when anterior third of tongue is irradiated. Alteration in saliva may account partly for this reduction, which may proceed to a state of virtual insensitivity, with recovery to near normal level, some 60 to 120 days after irradiation[15].

Teeth:

Irradiation of teeth with therapeutic doses during their development severely retards their growth. If it precedes calcification, irradiation may destroy the tooth bud. Irradiation after

calcification has begun may inhibit cellular differentiation causing malformations and arresting general growth.

Children receiving radiation therapy to the jaws may show defects in the permanent dentitions such as retained root development, dwarfed teeth or failure to form one or more teeth. In adults, dental pulp undergoes a decrease in vascularity with fibrosis and atrophy. Clinically, pulpal response to infection, trauma and dental procedures appears to be compromised.

Radiation caries is a rampant form of dental decay that may occur in individuals who receive a course of radiotherapy that includes exposure to salivary glands. The carious lesions result from changes in the salivary glands and saliva, including reduced flow, decreased pH, reduced buffering capacity and increased viscosity. Irradiation of teeth by itself does not influence the course of radiation caries.

Bone:

The primary damage to mature bone results from radiation induced damage to the vasculature of the periosteum and cortical bone. Radiation also acts destroying osteoblasts and to a lesser extent, osteoclasts. Ewing first described vascular irradiation injury in bones. He observed the formation of sclerotic connective tissue in the marrow cavity, obliterative endarteritis and periarteritis. Subsequent to radiation, normal marrow may be replaced with fatty marrow and fibrous connective tissue. The marrow tissue becomes hypovascular, hypoxic and hypocellular. When these changes are so severe, that bone death results, the condition is termed osteoradionecrosis.[15, 16,17]

RADIATION EFFECTS ON SALIVARY GLANDS:

Radiotherapy (RT) is commonly used to treat head-and-neck tumors. In these treatments, parotid, submandibular and minor salivary glands are often incidentally irradiated. Salivary gland parenchyma is very sensitive to radiation (the parotid gland is more sensitive compared with the submandibular gland).[21]

Radiotherapy alters the parenchymal structure and vascularity of salivary glands which result in volume and viscosity changes of secreted saliva.(2) Ionising radiation causes glandular tissue damage, which may result in a rapid, irreversible loss of salivary fluid secretion. The glandular architecture is replaced by ductal remnants and loose fibrous connective tissue which is moderately infiltrated with lymphocytes and plasma cells. This progressive glandular, atrophy, fibrosis and reduced salivary output begins slowly after initial exposure and intensifies thereafter.[22]

A reduction in salivary function is a common toxicity and reduces the patient's quality of life(QOL). Inadequate salivary function ("xerostomia") leads to multiple problems, including poor dental hygiene, a propensity to oral infections, sleep disturbances, oral pain, and difficulty chewing and swallowing. Stimulated salivary production is largely (60–70% of total) derived from the parotid glands, with the balance from other glands. Resting (unstimulated) salivary production is due primarily to the submandibular and sublingual glands and numerous small oral salivary glands.[23]

Saliva flow reduces by 50–60% during the first week of radiotherapy and after 6 weeks of radiotherapy and 60 Gy radiation it reaches 0%. This complication is more common among patients who receive bilateral radiotherapy.[24] According to **Deasy et al** Minimal gland function reduction occurs at <10–15 Gy mean dose. Gland function reduction

gradually increases at radiation doses of 20–40 Gy, with a strong reduction (usually by >75%) at >40 Gy.[22]

Radiation induced xerostomia:

Major salivary glands are situated at the lateral facial and submandibular regions where they are commonly included in to or close to the target volume in radiotherapy of oral cancers. Parotid glands are commonly irradiated with high radiation dose in conventional RT, as they are in close proximity to the radiation field. High radiation dose may damage salivary glands leading to xerostomia. Saliva is produced by acinar cells and drained to the excretory duct through ductal cells, and finally secreted in to the oral cavity.[25]saliva is mainly composed of water(99.5%) and other components(0.5%)including amylase, inorganic salts, mucin and bicarbonate.[26] It is important in the normal daily life since saliva is responsible for moistening and softening food during ingestion, protecting oral mucosa and teeth and breaking down starch by its amylase.

Xerostomia may seriously impair the health related quality of life of long time survivors after head and neck RT.[27, 28, 29] It is because xerostomia may lead to alterations in speech and taste, malnutrition and difficulty in mastication and deglutition (**Eisbruch et al**.(2003), **chambers et al.** (2004).Oral mucosal dryness can also change the oral pH level and predispose to mucosal ulcerations, fissures, dental caries and oral infection.[30,31]

According to **Eisbruch et al.** the radiation induced xerostomia is an irreversible complication for the parotid gland received with a mean dose of 26 Gy or above. The study suggested that a mean dose of 26 Gy was a threshold dose for parotid glands. Other studies showed different thresholds of radiation dose for parotid gland ranging from 20Gy to 40Gy.[32] some studies however suggested that irreversible xerostomia could occur with a mean dose of

over 60Gy.[33] Currently there are various methods for the assessment of post –RT salivary glands and xerostomia, include histological evaluation, sialometry, magnetic resonance imaging, scintigraphy ,computed tomography and ultrasonography.

ULTRASONOGRAPHIC EVALUATION:

The echogenecity of a tissue primarily relates to its stiffness, the chief source of which is collagen, the content and arrangement of collagen with in tissue is a major factor in modification of the manner and extent to which a tissue attenuates the acoustic wave. The applications of USG in head and neck region is for examination of the thyroid gland, the salivary gland, the eye, examination of fetal face and sonically guided surgery.

Ian R Wilson (1989)[34] concluded that USG imaging of the superficial structures of the head and neck region plays a significant part in the investigation of virtually all non acute superficial swelling and mass lesions. USG have got added advantage of enabling clearer definition of the tissues of the head and neck, better documentation of the range of clinical application, assessment of the accuracy of USG in predicting subsequent histopathologic findings. They have recommended that USG should be a part of the diagnostic equipment used in oral radiology.

In Europe and Asia, US is widely accepted as the first imaging method for assessment of lymph nodes and soft-tissue diseases in the head and neck, including major salivary glands.[35,36,37,38] As the head and neck region has a complex anatomic structure, a sound knowledge of sonographic anatomy and spatial relationships is crucial for reliable performance of the examination. Also, knowledge of the sonographic features of the most common diseases in this area is a requisite.

It is sometimes not possible to visualize examined lesions completely at US because of their location, penetrating to the deep lobe of the parotid gland or behind the acoustic shadow of the mandible. In these situations, performance of further imaging examinations—CT or MR imaging is warranted. Also, in cases of suspected malignant lesions, further diagnostic methods (ie, CT or MR imaging) should be applied to assess possible infiltration of bones or deep structures invisible at US (the base of the skull, parapharyngeal space) and to evaluate deep-lying lymph nodes.[39, 40, 41] On the other hand, dynamic scintigraphy is still the method of choice in functional evaluation of the salivary glands.[42, 43]

Ultrasonography is widely used in cancer imaging and screening as it is safe, non-invasive, inexpensive, highly available and carries no radiation hazard. Although US is commonly used in the assessment of salivary gland diseases neoplasms, sjogrens syndrome, sialadenitis and sialolithiasis, there is scant information in the literatures about the ultrasound evaluation post-RT changes in the salivary glands.

US allow visualization of whole submandibular gland, sublingual gland and the superficial lobe of the parotid gland. Deep lobe of parotid cannot be assessed by US because it is obscured by the acoustic shadow of the mandibular ramus.[44]In ultrasonogrphy a normal parotid gland appears as homogenous speckle pattern structure.[45] Parotid gland is markedly or slightly hyperechoic compared to the adjacent muscle, and the echogenecity is determined by the amount of fatty glandular tissue deposited in the gland.[46]Normal parotid lymphnodes are usually observed at the pre-auricle level or at the tail of the gland, which demonstrated as hypoechoic oval structures with or without hyperechoic central hilus.

A normal submandibular gland is ultrasonographically shown as triangular structures in the transverse scan plan. Similar to the parotid gland, the normal submandibular

gland appears as a homogenous structure and is markedly or slightly hyperechoic when compared to the adjacent muscle. The normal non dilated intra glandular ducts of the submandibular gland are rarely seen ultrasonographically.[12]

To the best of my knowledge there is only four studies which had documented the post-RT changes of salivary glands ultrasonographically. ying et al used high resolution ultrasound to compare the sonographic appearances of normal and post-RT parotid glands. They found the grey scale US could be used to assess the size, echogenicity and internal architecture of the parotids. The post-RT parotids appeared as a heterogenous structure, and were hypo or isoechoic relative to adjacent muscles, with multiple hyperechoic lines or spots and hypoechoic areas. The heterogenous appearance of the post –RT glands might be due to the patches of inflammatory infiltrate appearing as multiple hypoechoic areas, whilst the presence of hyperechoic lines or spots might reflect fibrosis.[47]Although this study documented the sonographic appearances of the post-RT parotid glands, the sample size was small. Moreover the study focused on the assessment of the parotid glands in nasopharyngeal carcinoma patients treated with conventional radiotherapy.

S C H Cheng et al.2011[48] did study on sonographic appearance of parotid glands in patients treated with intensity modulated radiotherapy or conventional RT for nasopharyngeal carcinoma and sonographic appearance of submandibular glands in patients treated with external beam radiotherapy for nasopharyngeal carcinoma based on study done by ying et al.2007. He assessed post radiotherapy changes in parotid glands and observed a heterogeneous appearance of parotid gland post radiotherapy. This was in contrast to homogenous echotexture in normal parotid glands.

Imanimognaddam et al. (2012)[24] who evaluated changes in parotid and submandibular glands 2 weeks and 6 weeks following radiotherapy and observed significant reduction in dimensions of glands. On ultrasound he found glandular texture became heterogenic, hypoechoeic and irregular following radiation exposure.

Dr Rithiga gindal et al.2015[49] did a similar study, ultrasonographic evaluation of salivary glands before radiotherapy and after completion of radiotherapy and found the results similar to S C H Cheng et al.(2011) and Imanimognaddam et al (2012).

Saliva is a complex mixture of fluids, with contributions from the major salivary glands (parotid submandibular and sublingual), the minor or accessory glands. The parotid, submandibular and sublingual are the major salivary glands which are located outside the oral cavity, encapsulated and with extended duct systems to discharge their secretions into the oral cavity.[54, 57, 63]

Mechanism of Secretion of Saliva

Saliva is formed in two stages: a primary secretion occurs in the acini, then modified as it passes through the ducts. The primary secretion is formed actively by the movement of sodium and chloride ions into the lumen, creating an osmotic gradient which leads to the passive movement of water. Other acinar components are added here before the fluid enters the duct, where sodium ions are actively reabsorbed (chloride follow passively to maintain electrical equilibrium) and bicarbonate ions are secreted.[50, 51]

The macromolecular components (amylase, mucous glycoproteins, etc) are formed in the usual way in the acinar cell endoplasmic reticulum, processed into secretory vesicles in the Golgi apparatus and are exported from the cell by exocytosis.

Composition of saliva:

Saliva is a dilute fluid, over 99% being made up of water. The concentrations of dissolved solids (organic and inorganic) are characterized by wide variation, both between individuals and within a single individual.

Inorganic constituents of whole saliva.[50, 53]

Sodium	13 – 80 mmol/L
Potassium	13 – 38 mmol/L
Calcium	0.2 – 4.7 mg/dl
Phosphorous	2- 23 mmol/L
Chloride	10 – 56 mmol/L
Bicarbonate	2 – 30 mmol/L
Fluoride	0.0005 – 0.005 mmol/L

Organic constituents of whole saliva:

Urea	2 – 6 mmol/L
Uric acid	0.2 mmol/L
Amino acids	1- 2 mmol/L

Glucose	0.05 mmol/L
Lactate	0.1 mmol/L
Fatty acids	10 mg/l

Macromolecules in whole saliva:

1	Total protein	1.4 – 6.4 gm/dl
2	α-Amylase	103–380 U/litre
3	Lysozyme	109 mg/l
4	Peroxidase	3 mg/l
5	IgA	194 mg/l
6	IgG	14 mg/l
7	IgM	2 mg/l
8	Lipid	20 – 30 mg/l

Normal flow rate of saliva

Unstimulated flow rate: 0.1 – 0.5 ml/min.

Stimulated: 1.1 – 3.0 ml/min.

Ph: 6.2 – 7.6.

Specific gravity – 1.002 – 1.008

PROPERTIES AND FUNCTIONS OF SALIVA[51, 52]

Digestion: Salivary amylase has been considered to be of significance for dental health because of its intraoral actions. However, starch digestion in the mouth may either be beneficial in aiding starch clearance, or detrimental in liberating maltose for fermentation by oral bacteria to form acid.

Salivary amylase initiates the digestions of starch, but is inactivated in the stomach because of the low pH and proteolytic activity there.

1) Lubrication:

The lubrication of the hard and soft oral surface is very important for speech, mastication and swallowing, and for general oral health and comfort. Saliva provides a tissue – coating film that is responsible for lubrications and bolus formation, a property, which is due to the water, and mucous glycoproteins it contains.

2) Dilution and Clearance:

The effect of water content of saliva is the dilution of substance introduced into the mouth, and their subsequent removal by swallowing or spitting.

3) Neutralisation and Buffering:

Saliva is alkaline and is an effective buffer system. These properties protect the oral tissues against acids from food or from plaque. The bicarbonate ion, present especially in stimulated salvia is responsible for this property. Besides bicarbonate, a small amount of buffering is provided by the phosphate ions and proteins of saliva.

4) Saturation:

Saliva is supersaturated with respect to tooth mineral. This is responsible for the growth of hydroxyapatite crystals during the remineralisation phase of the caries process. Sailva is also a source of fluoride for plaque and for uptake into carious lesions during de and remineralisation.

5) Antibacterial effects.

The principal action of salivary IgA is to aggregate specific bacteria and prevent their adhesion to oral hard and soft tissues.

Non – Specific antibacterial proteins

Lysozyme: An antibacterial enzyme, which attacks components of the cells wall of certain bacteria leading to lysis.

Lactoferrin: An iron binding protein, which removes free iron from saliva, depleting the supply of iron needed for bacterial growth.

Sialoperoxiase: Oxidises salivary thiocyanate ion to hypothiocyanate, a potent antibacterial substances.

6) Pellicle and plaque formation:

Both pellicle and plaque matrix contain glycoproteins predominantly derived from saliva, pellicle protects the teeth against chemical and mechanical insult.

Radiation effects on teeth:

Irradiation of teeth with therapeutic doses during their development severely retards their growth. If it precedes calcification, irradiation may destroy the tooth bud. Irradiation after calcification has begun may inhibit cellular differentiation causing malformations and arresting general growth.

Children receiving radiation therapy to the jaws may show defects in the permanent dentitions such as retained root development, dwarfed teeth or failure to form one or more teeth. In adults, dental pulp undergoes a decrease in vascularity with fibrosis and atrophy. Clinically, pulpal response to infection, trauma and dental procedures appears to be compromised.[18, 19,20]

Radiation caries is a rampant form of dental decay that may occur in individuals who receive a course of radiotherapy that includes exposure to salivary glands. The carious lesions result from changes in the salivary glands and saliva, including reduced flow, decreased pH, reduced buffering capacity and increased viscosity. Irradiation of teeth by itself does not influence the course of radiation caries.

Peter Moller et al, (2004)[59] conducted a study on 54 patients with advanced squamous cell carcinoma who were treated with radiation alone or in combination with surgery or chemotherapy or both. The flow rates, pH are buffering capacity were determined before during, and up to 12 months after the completion of radiation. The mean whole resting flow rates for all patients decreased gradually during irradiation (weeks 1 through 6.5) to 45%, 36%, 35% 33%, 32%, 30%, and 21% compared with mean pre RTH levels. The corresponding values for whole stimulated saliva were 39%, 29%, 25%, 22%, 21%, 18% and 14%.

EFFECT OF RADIATION ON PH OF SALIVA

Samuel Dreizen et al in 1976[56] monitored 30 patients who were given a course of cancer radiotherapy. The pH of stimulated whole saliva was collected from these patients and was measured by using a Corning Model 12 Research pH meter. They observed that there was a slight decrease in pH from a preradiation mean of 7.01 to a mean of 6.83 after 6 weeks of radiation.

T. Vuotila et al in 2002[58] studied the whole saliva samples of 39 head and neck cancer patients having radiation therapy, which were collected before, during and after radiation therapy. They found that the salivary flow rate, buffer capacity and pH decreased, and the levels of lactobacilli increased significantly during the first half of the radiation therapy. They correlated the endogenously activated salivary MMP – 9 with low salivary pH (P = 0.013).

Peter Moller et al in 2004[59] conducted a study on 54 patients with advanced squamous cell carcinoma who were treated with radiation alone or in combination with surgery or chemotherapy or both. The pH of whole stimulated saliva (WSS) and whole saliva resting saliva (WRS) was measured electromechanically by using an Orion pH meter 230 A and a Ross electrode model 81 – 35.

They observed that there was an initial drop in salivary pH after 1 week of irradiation. At the end of radiotherapy the mean pH for WSS was 7.05, lesser than the pre-radiotherapy value; where as pH for WRS was 6.97, which is slightly higher than its pre-radiotherapy value. The lowest mean pH values during the study were recorded of 3 months post-radiotherapy (corresponding 80.94% for WRS and 90% for WSS of the pre-radiotherapy mean pH).

EFFECT OF RADIATION ON SALIVARY AMYLASE AND PROTEIN

Tuula A. Makkonen et al in 1986[60] studied eleven patients treated for malignant conditions of the head and neck and analyzed the radiation induced changes in the flow rate and protein composition of stimulated whole saliva of these patients. Paraffin-stimulated whole saliva samples were collected once 2 to 21 days before therapy and then after 20, 40 and 60 Gy cumulative dose of irradiation. They found that salivary amylase activities decreased with increasing dose of radiation, especially when expressed as the amount of enzyme secreted per minute. Unusually high salivary concentrations of albumin, lactoferrin, lysozyme, salivary peroxidose, myeloperoxidase, and total protein were observed during the therapy, but most values slowly returned to pretreatment levels after cessation of radiation.

H. Valdez et al in 1992[57] evaluated fifty patients with radiation induced xerostomia and studied the effect of differential radiation on major salivary glands. Sialochemical analysis included total protein, lysozyme, lactoferrin, amylase, sodium, chloride and potassium. They investigated that the outputs per minute of protein, peroxidase, hexosamine, amylase, potassium, and calcium are significantly decreased during radiotherapy and up to 6 months after the end of treatment. The output of peroxidase potassium, calcium had returned to normal 18 months after radiotherapy whereas total protein, hexosamine and amylase were still significantly decreased.

Samuel Dreizen et al in 1976[56] monitored 30 patients who had undergo radiotherapy for head and neck malignancies. The salivary total protein was determined by Kingsley procedures. The mean value for salivary protein increased 0.53 mEq/L between the initial and final measurements and found that it was statistically meaningful ($P< 0.001$).

Dr Barres Pontes C et al in 2004[61], studied the clinical aspects and biochemical properties in the saliva of 21 patients prior to and following radiotherapy for head and neck cancer and compared with the same properties in a control group of 21 subjects free of cancer. The total salivary protein was determined by Bradford and method. Amylase activity was measured by reducing sugars released from a soluble starch substrate, quantified by the dinitrosalicylic method. No statistically significant alteration was observed in total salivary protein concentration. A statistically significant alteration was observed in total salivary protein concentration. A statistically significant reduction ($P < 0.01$) of salivary amylase activity (856.6 ng/mg) ± 88.0 before and 567.0 ng/mg ± 120.6 after irradiation) was observed.

Tomasik A et al in 1994[62] measured the serum and salivary alpha-amylase for controls and patients with laryngeal carcinoma, before and after localized irradiation including salivary glands. A significant increase in serum amylase was observed after irradiation. Alpha-amylase activity in saliva was decreased after irradiation but differences were not statistically significant due to the significant decrease of protein in saliva of irradiated group.

Brown LR et al in 1976[67] monitored the salivary and serum lysozyme, immunoglobulin, albumin and total protein levels in thirty patients with cancer of the head and neck before, during and after radiotherapy and compared with those of a group of non-irradiated non cancer control subjects. The mean volume-based saliva lysozyme and total protein concentrations were significantly higher in the cancer patients before radiotherapy than in the control group. During radiotherapy, the mean volume-based concentration of all protein components assayed increased as the saliva flow rate decreased.

Funegard U et al in 1994[55] studied the parotid saliva composition before, during and up to 18 months after the irradiation period in 16 cancer patients treated for malignancies in the head and neck region. Stimulated parotid saliva was collected prior to radiotherapy and when possible, weekly during treatment. Samples were taken 2, 4, 6, 12, and 18 months after the end of radiotherapy. The concentrations of the measured variables increased already during the first week of radiotherapy and at the end of the treatment period the concentrations for total protein, salivary peroxidase, hexosamine and salivary IgA were significantly increased. The concentrations for total protein, salivary peroxidase and salivary IgA were still increased 6 months after the end of irradiation. At the 18 months observation all concentrations had returned to normal, as evaluated in a paired t –test.

Nagler R et al in 1997[63] examined various sialochemical parameters in parotid and submandibular secreted saliva collected from irradiated rats. Various doses of radiation from 2.5 to 14 Gy were administered to the head and neck region and the saliva was evaluated for its amylase activity and the concentration of sodium, potassium, and total protein. The total protein concentrations of P saliva showed a radiation dose-dependent reduction at 3 days and 3 and 9 months following 15 Gy of 93%, 82%, and 73% ($P < 0.01$) respectively.

Ben Arych et al in 1975 [64] examined a group of 15 subjects and noted a marked increase in sodium concentration in unstimulated whole saliva despite the marked reduction in flow rate. They attributed the increase to the effect of irradiation on the resorptive system in the striated ducts of the salivary glands.

Donia sadri et al.2011[69] evaluated changes in the amount of saliva and its biochemicals (amylase, proteins, immunoglobulins and buffering capacity) in 18 patients before and after

radiotherapy. The study results showed overall reduction in pH and salivary amylase and increase in total protein after RT.

EFFECT OF RADIATION ON INORGANIC CONSTITUENTS (SODIUM, POTASSIUM, CALCIUM) OF SALIVA

Jay S. Cooper et al in 1994[65] described that the salivary flow continues the decline throughout a typical course of radiation treatment and may become barely measurable by the dent of a 6 – 8 week course. The decreased salivary viscosity, decreased pH, increased concentration of sodium, chloride, calcium, magnesium and protein and a decreased concentration of bicarbonate and IgA in the saliva.

Ingrid H. Valdez et al in 1992[57] evaluated fifty patients with radiation induced xerostomia. The compared the major salivary gland function with that of 50 non-irradiated controls. They showed that the sodium concentration in patient's saliva was increased but the difference was not statistically significant. The chloride content was significantly elevated for both parotid and SM/SL saliva (P = 0.0001). There were no difference in potassium concentration between patients and controls. They also showed that the patient's total protein concentration was not significantly different from that of controls.

Sameul Dreizen et al in 1976[56] monitored the saliva and serum electrolyte concentration in 30 patients, who were undergoing head and neck radiation treatment. They measured the salivary sodium and potassium by flame photometry method, calcium and magnesium by atomic absorption in a Unicam SP 1900 Atomic absorption spectrophotometer. The chloride and total protein were determined in a Beckman/ Spinco Ultramicro Analytical system by the ultra microadaptation of the Schales and Schales and Kingsley procedures

respectively. They showed that the mean increased 39.85 mEq/L in Na+, 20.35 mEq/L in $C1^-$, 1.29 mEq/L in Ca++ between the initial and final measurements and were all statistically meaningful ($P < 0.001$). They described that the large Xerostomia – related increase in salivary sodium and chloride and decrease in salivary bicarbonate found in their study reflected the radiation damage to both acinar and duct system.

Vissink A, et al in 1990[66] monitored the changes in the composition and rate of secretion of rat whole, parotid and submandibular / sublingual salvia after local irradiation of the salivary gland region with a single dose of 10 Gy. They collected salivary samples before and 1- 30 days after irradiation, after stimulation with pilocarpine maximum changes in the latent period, the flow rate and the composition of parotid, SM/SL saliva were observed three days after a radiation dose of 10 Gy. Partial recovery was seen for the latent period, (Pi), (Ca^{2+}) and concentration of amylase, whereas the flow rate and Na^+ remained low and K^+ remained high.

Shannon and Prigmore in April 1959[67] were collected Whole saliva samples from 270 healthy individuals. Sodium, potassium and chloride and volume were estimated. A positive correlation was found between volume and chloride and between volume and sodium while potassium was found to be independent flow rate.

Wu et al, in 1993[68] confirmed, there was no significant correlation when comparing young and aged healthy controls regarding salivary Na+ and K+ concentration in unstimulated saliva and stimulated saliva. No significant difference between Na+ and K+ concentration in the salivary secretion of healthy controls patients with similar flow rates was observed.

G Koshy et al.2011[70] studied whole saliva physio-biochemical changes and quality of life in head and neck cancer patients following conventional radiotherapy in 53 head and neck cancer patients, and the results demonstrated a significant decline, shift to more acidic pH, higher salinity, falling proteins and amylase concentrations at 6 weeks of RT.

MATERIALS AND METHOD

The study was conducted after getting approval from the Institutional Ethical Committee.

STUDY CENTRE:

1. **Department of Oral Medicine and Radiology**,

Tamil Nadu Government Dental College and Hospital,

Chennai – 600 003

2. **Bernard Institute of Radiology**,

Rajiv Gandhi Government Hospital,

Chennai -600003.

3.**Department of Biochemistry**

Rajiv Gandhi Government Hospital,

Chennai -600003

CASE SELECTION:

The study population include total of 30 patients, either of the sex who were diagnosed as oral squamous cell carcinoma based on clinical and histological findings.

Inclusion criteria:

- Patients with age group of 40-70 years , both gender
- Patients diagnosed as oral cancer in Dept.Oralmedicine and Radiology.TNGDC,Chennai and referred patients from Radiation oncology,RGGGH,Chennai.
- Patients who planned for Radiotherapy.
- Oral cancer patients who are willing to take part in the study.

Exclusion criteria:

- Patients not willing to participate in the study
- presence of associated diseases such as Sjogren' s disease, salivary gland masses, human immunodeficiency virus, diabetes mellitus, liver cirrhosis or autoimmune diseases.
- History of previous radiotherapy.
- Patients under prolonged drug therapy.

ARMAMENTARIUM REQUIRED FOR EXAMINATION (Fig.1)

- Mouth mirror
- Probe
- Tweezer
- Mask and glove

MATERIALS USED:

- Ultrasonographic machine
    1. PHILIPS clear Vue 350
    2. High frequency transducer 13-5
- Graduated sterile cup to collect unstimulated whole saliva
- Universal pH paper with range 2-10.5
- REMI R-8M Centrifugal machine
- EasyLyte Na/K analyzer
- ERBA 640 clinical chemistry discrete Random access Auto analyzer.

METHODOLOGY:

A total of 30 oral cancer patients who fulfilled the inclusion and exclusion criteria were selected for this study. Among the 30 patients 23 were males and 7 females. Age range of the patient was 30-70. All planned for conventional radiation treatment with cobalt 60 apparatus in the department of radiation Oncology, RGGGH, Chennai for carcinoma of the oral cavity. Field of RT unilateral or bilateral. The treatment planned for 5 days in a week. The weekly dosage was 10 Gy (gray). The total dosage given varied from 60 to 66 Gy and administered over a period of 6 to 7 weeks.

Ultrasonographic evaluation of 60 parotids and 60 submandibular glands were done prior to radiotherapy and six weeks after completion of radiotherapy to evaluate the length, width, depth, echotexture, echogenicity, and vascularity of salivary glands.

In the ultrasound examination, patients laid supine on the examination bed, with neck extended, the right & left parotid glands, and right & left submandibular glands were assessed

separately with the patients head turned away from the side of examination. Sonographical evaluations were performed by an expert radiologist at Bernard Institute of Radiology, Rajiv Gandhi Government Hospital in two stages: I, prior to the radiotherapy; stage II, six weeks after radiotherapy. Length, width and depth were measured for each parotid and submandibular gland

To evaluate the length of the parotid gland, the probe was situated longitudinally behind the ramus of the mandible and the maximum value was measured.

To evaluate the length of submandibular gland, the probe was situated parallel to the inferior edge of the mandible and the maximum value was measured. The widths of parotid and submandibular glands were also measured by placing the probe vertically in the middle of the ramus of the mandible and vertically to the body of the mandible, respectively, and the maximum values were measured. The depth was identified as the distance between the retromandibular vein and the gland capsule.

Gland margins, echogenicity and echotexture were also evaluated. Echogenicity is described as hyperechoic (denoting a region in an ultrasound image in which the echoes are stronger than normal or than surrounding structures), isoechoic (a region in an ultrasound image in which the echoes are similar to the surrounding region) and hypoechoic (a region in an ultrasound image in which the echoes are weaker or fewer than normal or than in the surrounding heterogeneous. Gland margins were considered as regular or irregular. Vascularity assessed qualitatively by seeing the number of vessels present in a particular region and evaluated as normal or decreased.

COLLECTION OF SALIVA

Unstimulated Whole saliva was collected under resting conditions in a quiet room, between 8 am and noon, at least 1 hour after food intake .Patients asked not to swallow and to generate saliva in their mouths and to spit into a sterile cup for 5 minutes on the the same day of ultrasound, before RT and six weeks after completion of RT. After collection, pH was tested at once by using pH paper and the rest of the saliva was stored in deep freezer for further biochemical analysis. . For patients who had very sparse saliva secretion, the saliva collection time was extended to 15 minutes.

Method of testing pH of saliva

The pH of saliva should always be tested immediately after collection, because the p may change due to loss of CO_2 on storage.

PROCEDURE:

The stimulated saliva was collected from patients as mentioned earlier. The pH indicator strip was placed into the sample of saliva for 10 seconds. Then the colour of the strip was checked and compared with the testing chart provided in the pH strip book . The range of pH from 2.0 to 10.5 can be checked using this saliva pH strip.

- REMI R-8M Centrifugal machine

Procedure: The sample was transferred to the appropriate test tube and centrifugation done at 3000 rpm for 10 minutes.

ESTIMATION OF SALIVARY SODIUM AND POTASSIUM:

Method: EasyLyte Na/K analyzer. Medica Corporation.

Principle: Ion selective Electrode.

PROCEDURE:

The centrifuged saliva sample is alliquoted and placed in to the analyser the results were displayed .

Reference range:

Sodium- 2-21mmol/l

Potassium- 10-36mmol/l

ESTIMATION OF SALIVARY CALCIUM, AMYLASE AND TOTAL PROTEIN: PROCEDURE:

The centrifuged sample was placed in the sample tray of ERBA 640 clinical chemistry discrete Random access Auto analyser for analysis and the results were displayed in the screen.

METHOD OF SALIVARY CALCIUM ESTIMATION IN ERBA 640:

PRINCIPLE

Arsenazo III combines with calcium ions at pH 6.5 to form a coloured chromophore, the absorbance of which is measured at 650 nm (650-660 nm) and is proportional to calcium concentration. Arsenazo III has a high affinity (k° = 1 x 10 -7) for calcium ions and shows no interference from other cations normally present in serum, plasma or urine.

REAGENT COMPOSITION

R1

Arsenazo III- 0.10 mmol/l

Phosphate buffer (pH 7.8 ± 0.1) 50 mmol/l

R2 standard

Measuring range: 0.6 – 16 mg/dl

Reference range:1.2-2.8mmol/l

METHOD OF ESTIMATION OF SALIVARY ALPHA AMYLASE IN ERBA 640

PRINCIPLE

2-Chloro-4-nitrophenol-β -1- 4 galactopyranosylmaltotrioside (CNP-G) is a direct substrate for determination of α-amylase activity, which does not require the presence of ancillary enzymes. The rate of 2-chloro-4-nitrophenol formation can be monitored at (400-420) nm and is proportional to the α-amylase activity.

Gal – G2 - α-CNP----------> Gal – G2 + CNP

REAGENT COMPOSITION

R1

MES buffer 50 mmol/l

Calcium Chloride 3.81 mmol/l

Sodium Chloride 300 mmol/l

Potassium Thiocyanate 450 mmol/l

Sodium Azide 13.85 mmol/l

CNPG 0.91 mmol/l

Measuring range: 10.8 – 1500 U/l

Reference range: 27 ± 3 - 144 ± 160 U/l

METHOD OF ESTIMATION OF SALIVARY TOTAL PROTEIN IN ERBA 640:

PRINCIPLE

Biuret method. The peptide bonds of protein react with copper II ions in alkaline solution to form a blue-violet ion complex, (the so called biuret reaction), each copper ion complexing with 5 or 6 peptide bonds. Tartrate is added as a stabilizer whilst iodide is used to prevent auto-reduction of the alkaline copper complex. The colour formed is proportional to the protein concentration and is measured at 546 nm (520-560).

REAGENT COMPOSITION

R1

Copper II Sulphate 12 mmol/l

Potassium Sodium Tartrate 31.9 mmol/l

Potassium Iodide 30.1 mmol/l

Sodium Hydroxide 0.6 mol/l

R2 standard

Measuring range: 0.37 – 15 g/dl

Reference range:1.4-6.4g/dl

1. ARMAMENTARIUM

2. USG MACHINE

3.CENTRIFUGAL APPARATUS

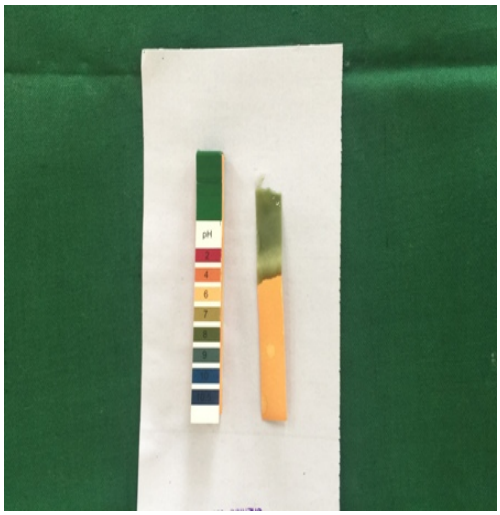
4.EASYLYTE

5. ERBA 640

6. ERBA KIT

7. CALCIUM KIT

8. PH STRIP



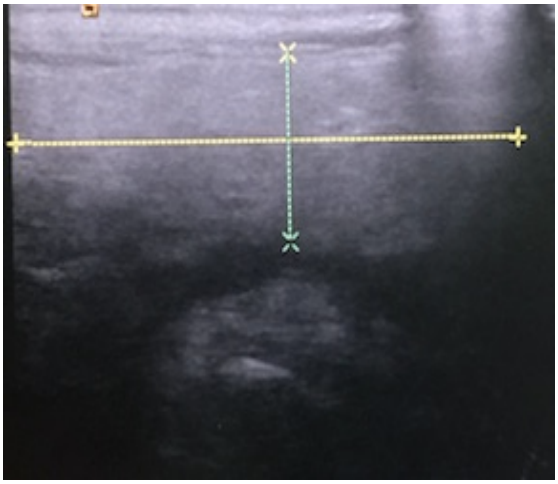
9. PRE RADIOTHERAPHY

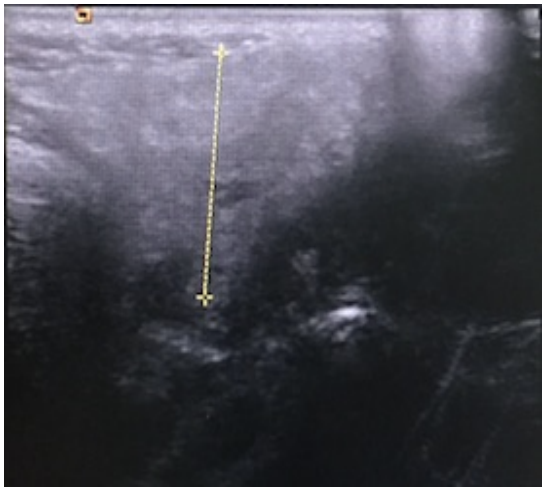
10.POST RADIOTHERAPHY

11. COBALT 60 APPARATUS

12. USG EVALUATION

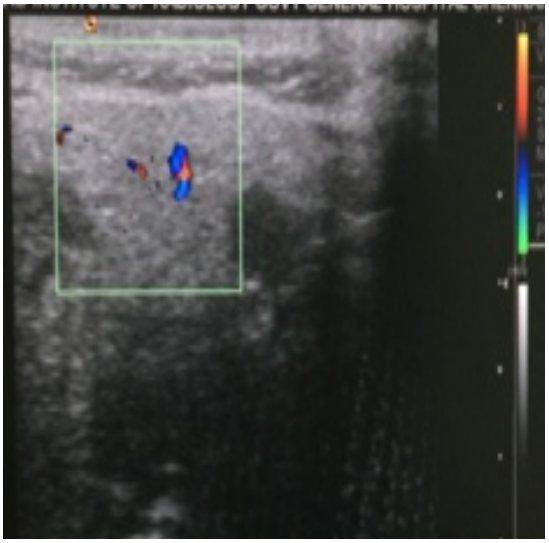
13. LENGTH, WIDTH, DEPTH, MARGIN, ECHOTEXTURE AND ECHOGENICITY OF RIGHT PAROTID-PRE RT



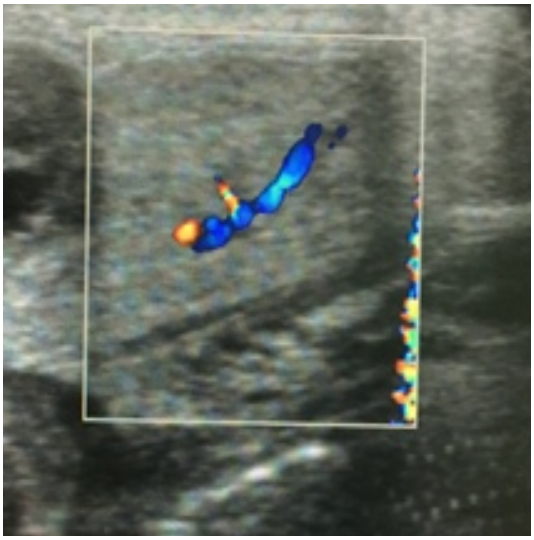


14. VASCULARITY –PRE RT

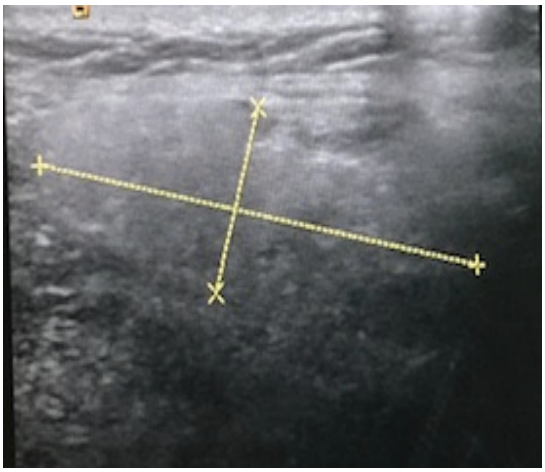
RIGHT PAROTID

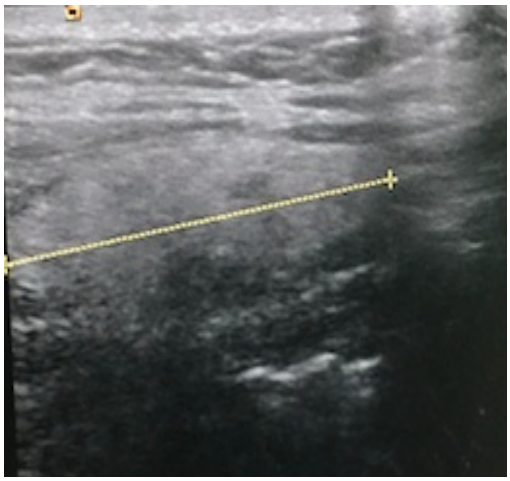


RIGHT SUBMANDIBULAR

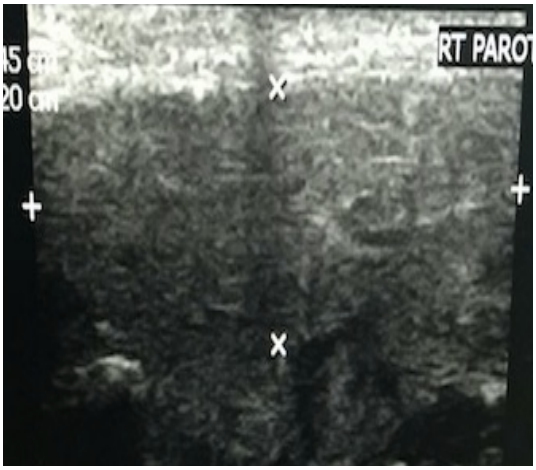


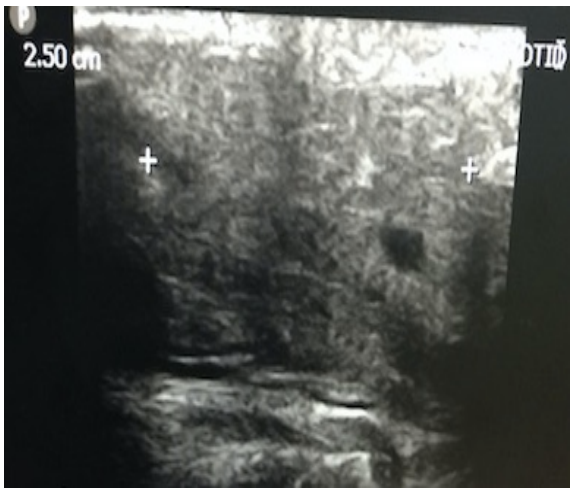
15. LENGTH, WIDTH, DEPTH, MARGIN, ECHOTEXTURE, ECHOGENICITY OF RIGHT SUBMANDIBULAR GLAND-PRE RT





16. LENGTH, WIDTH, DEPTH, MARGIN, ECHOTEXTURE, ECHOGENICITY OF RIGHT PAROTID -POST RT

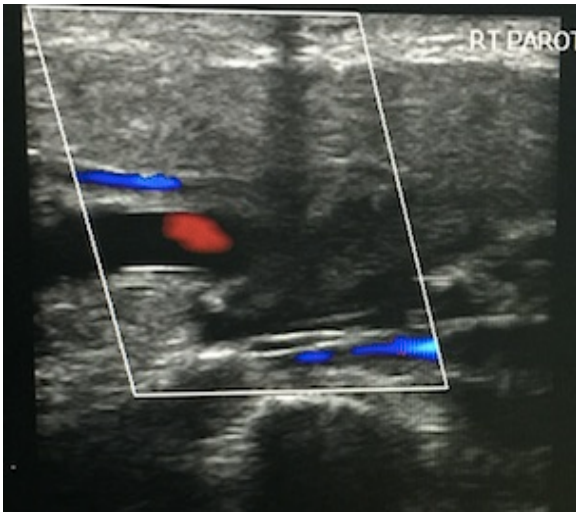




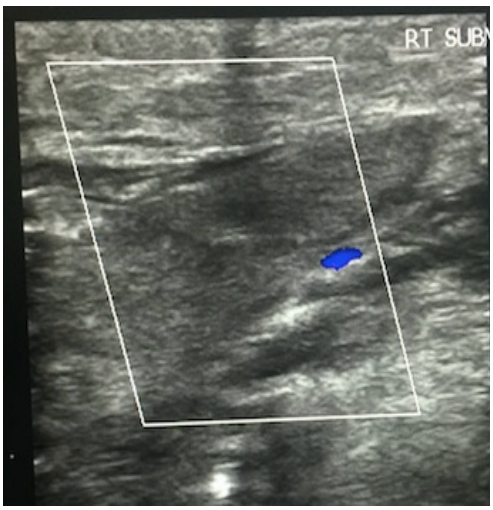
17. LENGTH, WIDTH, DEPTH,MARGIN, ECHOTEXTURE, ECHOGENICITY OF RIGHT SUBMANDIBULAR-POST RT

18. VASCULARITY-POST RT

RIGHT PAROTID



RIGHT SUBMANDIBULAR



STATISTICAL ANALYSIS:

Statistical analysis was done by computer software program SPSS 18.01.

Paired sample t test was conducted to assess the level of significance of the differences in size (length, width & depth) and Pearson chi-square test was conducted to assess the level of significance of the difference in margin, echo texture, echogenicity and vascularity of Parotid and submandibular salivary glands in oral cancer patients before and after radiotherapy. Paired sample t test was used to assess the level of significance of difference in biochemical changes of saliva before and six weeks after radiotherapy. Association of TNM staging with quantitative variables was done by using one way ANOVA. Pearson chi-square test was conducted to analyze the association of TNM staging with qualitative variables margins, echo texture, echogenicity, and vascularity.

RESULTS

Total 30 patients with oral carcinoma who fulfilled the inclusion and exclusion criteria were selected for the study. Out of 30 patients 23 males (76.7%) and 7 females (23.3%) were present. The maximum age of the patient was 70, and the minimum was 30,with a mean 51.3. The given dose was minimum 60 Gy, maximum 66 Gy with a mean 63.6.

Out of 30 patients 20% patients were having carcinoma on right buccal mucosa, 6.7% patients were having carcinoma on left buccal mucosa, 13.3% patients on anterior 2/3 rd of tongue,13.3% patients on right lateral surface of the tongue, 16.7% patients were having carcinoma on floor of the mouth,3.3% patients were having on right side alveolus and hard palate, 6.7% patients were having carcinoma on right buccal mucosa and floor of the mouth,10% patients were having carcinoma on anterior 2/3 rd of the tongue and floor of the mouth,3.3% patients were having on right buccal mucosa and right alveolus,3.3% patients left buccal mucosa and retromolar region, and 3.3% of patients having carcinoma on left side alveolus, hard palate and retromolar trigone.

A total of 60 parotid glands and 60 submandibular glands were evaluated with ultrasonography in 30 patients treated with conventional RT before and six weeks after radiotherapy.

Pre radiotherapy (stage I) ultrasonographic evaluation of right parotid gland showed the mean length of 3.3±0.6,width 1.8±0.7,depth 1.9±0.7 .Post radiotherapy (stage II) ultrasoographic evaluation of right parotid gland showed that the mean length ,width, and depth dimensions were significantly reduced to 2.5±0.6,1.2±0.3,1.3±0.4 respectively . Showed statistically significant P value 0.000

Likewise stage I left parotid gland mean length 3.2±0.6, width 1.5±0. depth1.7 ±0.9 significantly reduced in to mean length 2.6 ±0.5, width 1.2 ±0.5, depth1.3 ±0.4 in stage II. Stage I USG evaluation of right submandibular gland showed mean length 3 ±0.3,width 1.3 ±0.6,depth 1.7 ±0.6 which significantly reduced in stage II as 2.3 ±0.4,1 ±0.2,1.2 ±0.4 respectively. Left submandibular gland showed mean length 2.9 ±0.3,width 1.3 ±0.3,depth1.6 ±0.8 in I stage USG evaluation. On stage II evaluation mean length 2.4 ±0.3,width ±2.4,and depth1.2 ±0.4

We found the results were statistically significant P value0.000(P<0.005) Results showed that there was a highly significant reduction the mean length, width, depth dimension of the right parotid gland, left parotid gland, right submandibular gland before and six weeks after radiotherapy. However there was statistically significant difference in the mean length, mean depth dimensions, of the left submandibular gland, mean width dimension showed no significant difference.

There was a significant difference present in margin, echotexture and echogenicity, and vascularity in both right and left parotid glands& right and left submandibular glands. In stage I ultrasonographic evaluation of right parotid gland showed 100% of regular margin. In stage II 10% of patients showed regular margins, 90% of the patients showed irregular margins of the gland. In stage I left parotid evaluation 100% patients showed regular margins which had been turned irregular (100%) in stage II.

Ultrasonographic evaluation of right submandibular gland revealed 100% of patients had regular margins in stageI. In stage II, 53.3%% patients had regular margins and 46.7% patients showed irregular margin of the right submandibular gland. In stage I evaluation of left

submandibular gland 100% patients showed regular margins of the gland, in stage II,63% patients showed irregular margin. We found the results were statistically significant P value 0.000 (P<0.005). This result showed that there were significant changes in the margin after radiotherapy when compared to pre radiotherapy.

With respect to glandular texture, both the salivary glands (right & left) on Ultrasonography showed homogenous echotexture before radiotherapy. In stage I 100% patients having homogenous echotexture in right parotid and left parotid. On evaluation of stage II, 6.7% patients showed homogenous echotexture, 93.3% patients showed heterogenous echotexture in right parotid gland, and 100% patients showed heterogenous echotexture in left parotid gland. On evaluation of right submandibular gland 100% patients showed homogenous echotexture in stage I. On stage II 16.7% of patients showed homogenous echotexture, and 83.3% patients showed heterogenous echotexture. On evaluation of left submandibular gland 100% patients showed homogenous echotexture .On stage II 70% of patients showed heterogenous echotexture and 30% of patients showed homogenous echotexture. On the whole, on ultrasonography both the salivary glands showed homogenous echotexture before radiotherapy, which significantly changed to heterogenous echotexture six weeks following radiotherapy. We found the results were statistically significant P value 0.000 (P<0.005).

All the patients (100%) showed hyperechoic echogenicity in both the glands before radiotherapy on ultrasound.16.7% of patients showed isoechoic echogenicity ,On evaluation of the glands six weeks after radiotherapy, 83.3% of people showed hypoechoic echogenicity in right parotid, 20%of patients showed isoechoic echogenecity and 80%of patients showed hypoechoic echogenicity in left parotid, 46.7% patients showed hyperechoic

echogenicity, 33.3% patients showed isoechoic echogenicity, 20% patients showed hypoechoic echogenicity in right submandibular gland, 10% patients showed hyperechoic, 20% patients showed isoechoic echogenicity,70% patients showed hypoechoic echogenicity in left submandibular gland. On overall echogenicity of the glands significantly changed from hyperechoic to hypoechoic before radiotherapy and six weeks after radiotherapy. We found the results were statistically significant P value 0.000 (P<0.005).

Both the parotid and submandibular glands were evaluated qualitatively by color doppler .Pre radiotherapy color doppler evaluation revealed 90% of patients showed normal vascularity, 10% of patients showed decreased vascularity. On stage II, 73.3% showed normal vascularity, and 26.7% patients showed decreased vascularity. On evaluation of left parotid 90%patients showed normal vascularity, 10%patients showed decreased vascularity. In stage II, 66.7% patients showed normal vascularity and 33.3% showed decreased vascularity .90% patients showed normal and 10% patients showed decreased vascularity on pre radiotherapy evaluation of right submandibular gland. On post radiotherapy evaluation, 80% showed normal and 20% showed decreased vascularity on post radiotherapy evaluation.90%of patients showed normal vascularity and 73.3% patients showed normal, 26.7% showed decreased vascularity on post radiotherapy color Doppler evaluation. There was an insignificant difference in vascularity between pre and post radiotherapy salivary glands when evaluated qualitatively by color Doppler.

Salivary biochemical analysis:

In the 30 oral cancer patients, the minimum value of salivary pH was 6 and maximum pH value was 7 before radiation. The pre radiation mean value of salivary pH was

6.5±0.5.Salivary pH was assessed in the same patients after six weeks of completion of radiotherapy. The minimum salivary pH observed was 5,and the maximum pH was 6,the mean value of salivary pH was 5.2±0.4.There was a statistically significant reduction in the pH before radiation and six weeks after completion of radiation.

Estimation of salivary sodium before radiation in 30 oral cancer patients revealed a minimum value of10.7 mmol/l and a maximum level of 36.4 mmol/ l. A mean of 19.5±6 mmol/ l was observed.

Estimation of level of sodium in the saliva in the same 30 study subjects after six weeks of radiation, revealed a minimum value of 17.8 mmol/ l and a maximum value of 69.4 mmol/ l. A mean value of 43.7±12.1 mmol/ l was observed. There was a significant increase in the salivary sodium the level b/w pre radiation and after 6 weeks of radiation (P = 0.000).

The level of salivary potassium was assessed in 30 study subjects prior to radiation. The minimum level of salivary potassium of 11.2 mmol/l and maximum level of 32.2 mmol/l was observed. The mean value of 18.4±5 mmol/l was noted (Table-

Estimated of salivary potassium after 6 weeks of radiation in the same 30 study subjects showed a minimum value of 9.11 mmol/l and a maximum value of 31.2 mmol/l. The mean value of salivary potassium of 16.9±5.1 mmol/l was observed. There was a significant decrease in the level of potassium in the whole saliva between preradiation and after 6 weeks of radiation (P=0.000).

The level of salivary calcium was estimated for 30 study subjects before radiotherapy. The minimum value of salivary calcium of 1.8 mg/dl, a maximum value of 5.2 mg/dl and a mean value of 3.6±0.8 mg/dl was observed (Table- 5).

Estimation of calcium in the whole saliva of the same 30 study subjects after 6 weeks of radiotherapy showed a minimum level of 2.4 mg/dl and a maximum level of 6.4 mg/dl. The mean value of 4.7±1.1 mg/dl was observed. There was a significant increase in the level of salivary calcium between preradiation and after 6 weeks of radiation was noted, (P=0.000)

Estimation of salivary amylase before radiation in 30 oral cancer patients showed a minimum value of 116.2U/L and a maximum value was 1109U/L. the mean value observed was 310±174.1.Estimation of salivary amylase in the same 30 patients six weeks after completion of Radiotherapy showed minimum value of 15.4,maximum value of 487.12 and the observed mean value was 46.2±102.6.There was statistically significant(P=0.000) reduction in mean values between pre radiotherapy and post radiotherapy salivary amylase estimation denoted that salivary amylase level was significantly reducing following radiotherapy in this study.

The salivary total protein measured in this study in 30 oral cancer patients before radiotherapy showed the minimum value of 1.13g/dl, the maximum value 2.53g/dl and the mean value was 1.5±0.3.The salivary total protein measured six weeks after completion of radiotherapy showed the minimum values of 1.34g/dl and the maximum value was 2.61g/dl. The mean value was 1.8±0.3.There was a statistically significant increase in the values between pre and post radiotherapy estimation of salivary total protein. In this study salivary protein level was significantly increased following radiotherapy.

Correlating TNM staging of tumor with pre and post radiotherapy, Ultrasonographic salivary gland show changes as:

Length, width, depth

In this present study, TNM staging was grouped according to tumor size as group I, Group II and group III for the ease of comparison. We evaluated the correlation of TNM staging of the tumor with pre and post radiotherapy salivary gland changes.

When evaluated length of right parotid showed mean length of 3.5±0.4 in group I, 3.0±0.6 in group II,and 3.3±0.2 in group III before radiotherapy. The P value for intergroup was 0.08 which was insignificant. The mean length of right parotid after radiotherapy was 2.7±0.5 for group I,2.3±0.7 for group II,and2.4± 0.3 in group III.P value for intergroup was 0.23,which was insignificant. The mean length of left parotid for group I was 3.4±0., for group II 3.1±0.6,for group III 3.1±0.6 when evaluating with pre radiotherapy values, and the p value for intergroup. The mean length of left parotid after completion of radiotherapy, for group I 4.8±6.3,for group II 2.4± 0.6,for group II I2.4±0.3 and the p value for intergroup was 0.06 which was insignificant. While evaluating right sub mandibular gland, it showed mean length of3.6±0.2 for group I,3±0.3 for group II,2.9±0.4 for group III for before radiotherapy. And post radiotherapy showed 2.4±0.2 for group I,2.1±0.4 for group II,2.2±0.3 and the p value for intergroup value was 0.35 which was insignificant.

When evaluated length of left submandibular showed mean of 3.0±0.2 in group I, 2.9±0.3 in group II, and 2.9±0.4 in group III before radiotherapy. The P value for intergroup was 0.7 which was insignificant. The mean length of left submandibular gland after

radiotherapy was 2.5±0.3 for group I,2.5±0.2 for group II,and2.3± 0.4 in group III.P value for intergroup was 0.53,which was insignificant.

When evaluated width of right parotid showed mean of 2.0±0.7 in group I, 1.6±0.6 in group II, and 1.9±0.26in group III before radiotherapy. The P value for intergroup was 0.36 which was insignificant. The mean width of right parotid after radiotherapy was 1.1±0.2 for group I, 1.1±0.3 for group II,and1.3± 0.3 in group III.P value for intergroup was 0.29,which was insignificant. When evaluated width of left parotid showed mean of 1.7±0.7 in group I, 1.4±0.8 in group II, and 1.4±0.2 in group III before radiotherapy. The P value for intergroup was 0.6 which was insignificant. The mean length of left parotid after radiotherapy was 1.3±0.5 for group I, 1.1±0.4 for group II,and1.2± 0.4 in group III.P value for intergroup was 0.23,which was insignificant.

While evaluating right sub mandibular gland, it showed mean length of3.6±0.2 for group I,3±0.3 for group II,2.9±0.4 for group III for before radiotherapy. And post radiotherapy it showed 2.4±0.2 for group I, 2.1±0.4 for group II, 2.2±0.3 and the p value for intergroup value was 0.35, which was insignificant. While evaluating left sub mandibular gland, it showed mean width of 1.3±0.3 for group I,1.2±0.3 for group II,1.5±0.3 for group III for before radiotherapy. The p value for intergroup was 0.311.And post radiotherapy it showed 1.1±0.2 for group I,0.9±0.1 for group II,2.9±0.5 and the p value for intergroup value was 0.20 which was insignificant.

When evaluated depth of right parotid showed mean of 2.1±0.74in group I, 2.0±0.7 in group II, and 1.4±0.6in group III before radiotherapy. The P value for intergroup was 0.06 which was insignificant. The mean depth of right parotid after radiotherapy was 1.4±0.2 for

group I, 1.5±0.5 for group II,and1.1± 0.3 in group III.P value for intergroup was 0.11,which was insignificant. When evaluated depth of left parotid showed mean of 1.8±0.5 in group I, 1.8±0.7 in group II, and 1.3±0.4 in group III before radiotherapy. The P value for intergroup was 0.13 which was insignificant. The mean depth of left parotid after radiotherapy was 1.4±0.4 for group I,1.3±0.5 for group II,and1.1± 0.2 in group III.P value for intergroup was 0.35,which was insignificant.

While evaluating right sub mandibular gland, it showed mean depth of 1.7±0.4 for group I,1.8±0.8 for group II,1.2±0.2 for group III for before radiotherapy and the p value for intergroup value was 0.12 which was insignificant..On analyzing post radiotherapy values it showed 1.3±0.4 for group I,1.3±0.4 for group II,1.0±0.4 and the p value for intergroup value was 0.35 which was insignificant. While evaluating left sub mandibular gland, it showed mean depth of 1.8±1 for group I,1.5±0.5 for group II,1.4±0.4 for group III for before radiotherapy. The p value for intergroup was 0.63.And post radiotherapy it showed 1.2±0.1for group I,1.0±0.2 for group II,1.1±0.4 and the p value for intergroup value was 0.27 which was insignificant.

On the whole although there was a highly significant difference present between preradiotherapy and post radiotherapy quantitative values of length, width, depth of right and left parotid and submandibular salivary glands there was not much difference in these parameters between TNM group I, group II, and group III which was divided based on tumor size. All the qualitative values including margins, echo texture, echogenicity and vascularity showed insignificant p value denoted that there was not much difference in these parameters between TNM groups.

TABLE 1: AGE DISTRIBUTION

SEX	AGE				TOTAL
	30-40	40-50	50-60	60-70	
MALE	4	6	6	7	23
FEMALE	1	2	0	4	7

TABLE 2: SITE OF LESION AND ITS FREQUENCY

SITE	FREQUENCY	VALID PERCENT
Rt Buccal Mucosa	6	20.0
Left Buccal Mucosa	2	6.7
Ant 2/3rd of tongue	4	13.3
Rt Lateral Surface of Tongue	4	13.3
Floor of the mouth	5	16.7
Rt side Alveolus/ Hard Palate	1	3.3
Rt Buccal Mucosa + Floor of Mouth	2	6.7
Ant 2/3rd of tongue + FOM	3	10.0
Rt BM and RT Alveolus	1	3.3
Lft BM AND RMT	1	3.3
Left side alveolus and hard palate + RMT	1	3.3

TABLE 3: TNM STAGING AND ITS FREQUENCY

STAGE	FREQUENCY	VALID PERCENT
T2 N0 M0	3	10.0
T2 N0 M0	1	3.3
T2 N1 M0	4	13.3
T2 N2 M0	2	6.7
T2 N2b M0	1	3.3
T2N2cM0	1	3.3
T3N1M0	6	20.0
T3N2M0	2	6.7
T3N3M0	2	6.7
T4N0M0	3	10.0
T4N1M0	2	6.7
T4aN2bM	1	3.3
T4bN1M0	1	3.3

TABLE 4: COMPARISION OF PRE & POST RT DIMENSIONS OFSALIVARY GLANDS

Gland	Dimension	Stage	Mean±S.D	P value
Right parotid	Length	I	3.3±0.6	0.000
		II	2.5±0.6	
	Width	I	1.8±0.7	0.000
		II	1.2±0.3	
	Depth	I	1.9±0.7	0.000
		II	1.3±0.4	
Left Parotid	Length	I	3.2±0.6	0.000
		II	2.6±0.5	
	Width	I	1.5±0.7	0.000
		II	1.2±0.5	
	Depth	I	1.7±0.6	0.000
		II	1.3±0.4	
Right submandibular	Length	I	3.0±0.3	0.000
		II	2.3±0.4	
	Width	I	1.3±0.6	0.000
		II	1.0±0.2	
	Depth	I	1.7±0.6	0.000
		II	1.2±0.4	
Left submandibular	Length	I	2.9±0.3	0.000
		II	2.4±0.3	
	Width	I	1.3±0.3	0.788
		II	1.4±2.4	
	Depth	I	1.6±0.8	0.000
		II	1.2±0.2	

I - Pre radiotherapy, II – Six weeks after radiotherapy

TABLE 5:COMPARISION OF PRE & POST RT CHANGES IN MARGINS OF SALIVARY GLANDS

GLAND	STAGE	MARGIN		P VALUE
		REGULAR (n%)	IRREGULAR (n%)	
RIGHT PAROTID	I	30(100%)	0(.0%)	0.000
	II	3(10%)	27(90%)	
LEFT PAROTID	I	30(100%)	0(.0%)	0.000
	II	0(.0%)	30(100%)	
RIGHT SUBMANDIBULAR	I	30(100%)	0(.0%)	0.000
	II	16(53.3%)	14(46.7%)	
LEFT SUBMANDIBULAR	I	30(100%)	0(.0%)	0.000
	II	19(63.3%)	11(36.7%)	

I - Pre radiotherapy, II – Six weeks after radiotherapy

TABLE 6: COMPARISION OF PRE & POST RT CHANGES IN ECHOTEXTURE OF SALIVARY GLANDS

GLAND	STAGE	ECHOTEXTURE		P VALUE
		HOMOGENOUS (n%)	HETEROGENOUS (n%)	
RIGHT PAROTID	I	30(100%)	0(0.0%)	0.000
	II	2(6.7%)	28(93.3%)	
LEFT PAROTID	I	30(100%)	0(0.0%)	0.000
	II	0(0.0%)	30(100%)	
RIGHT SUBMANDIBULAR	I	30(100%)	0(0.0%)	0.000
	II	5(16.7%)	25(83.3%)	
LEFT SUBMANDIBULAR	I	30(100%)	0(0.0%)	0.000
	II	9(30%)	70(100%)	

I - Pre radiotherapy, II – Six weeks after radiotherapy

TABLE 7: COMPARISION OF PRE & POST RT CHANGES IN ECHOGENICITY OF SALIVARY GLANDS

GLAND	STAGE	ECHOGENICITY			P VALUE
		HYPER ECHOIC	ISO ECHOIC	HYPO ECHOIC	
RIGHT PAROTID	I	30(100%)	0(0.0%)	0(0.0%)	0.000
	II	0(0.0%)	5(16.7%)	25(83.3%)	
LEFT PAROTID	I	30(100%)	0(0.0%)	0(0.0%)	0.000
	II	0(0.0%)	6(20%)	24(80%)	
RIGHT SUB-MANDIBULAR	I	30(100%)	0(0.0%)	0(0.0%)	0.000
	II	14(46.7%)	10(33.3%)	6(20%)	
LEFT SUB-MANDIBULAR	I	30(100%)	0(0.0%)	0(0.0)	0.000
	II	3(10%)	6(20%)	21(70%)	

I - Pre radiotherapy, II – Six weeks after radiotherapy.

TABLE 8: COMPARISION OF PRE & POST RT CHANGES IN VASCULARITY OF SALIVARY GLANDS

GLAND	STAGE	VASCULARITY		P VALUE
		NORMAL	DECREASED	
RIGHT PAROTID	I	27(90%)	3(10%)	0.181
	II	22(73.3%)	8(26.7%)	
LEFT PAROTID	I	27(90%)	3(10%)	0.06
	II	20(66.7%)	10(33.3%)	
RIGHT SUBMANDIBULAR	I	27(90%)	3(10%)	0.472
	II	24(80%)	6(20%)	
LEFT SUBMANDIBULAR	I	27(90%)	3(10%)	0.181
	II	22(73.3%)	8(26.7%)	

I - Pre radiotherapy, II – Six weeks after radiotherapy

TABLE 9: SALIVARY BIOCHEMICAL CHANGES

VALUES	STAGE	MEAN±S.D	P VALUE
pH	I II	6.5±0.5 5.2±0.4	0.000
Sodium	I II	19.5±6 43.7±12.1	0.000
Pottasium	I II	18.4±5 16.9±5.1	0.000
Calcium	I II	3.6±0.8 4.7±1.1	0.000
Salivary amylase	I II	310±174.1 46.2±102.6	0.000
Total protein	I II	1.5±0.3 1.8±0.3	0.000

I - Pre radiotherapy, II – Six weeks after radiotherapy

TABLE 10: GROUPING OF TNM STAGES

GROUPS	GROUP I	GROUP II	GROUP III
TNM STAGES	T_2 N_2 M_0	T_3N_2c M_0	T_4 N_0 M_0
	T_2 N_0 M_0	T_3N1 M_0	T_4N1 M_0
	T_2 N_0 M_0	T_3 N_2 M_0	T_4aNb M_0
	T_2N1 M_0	T_3N_3 M_0	$T_{4b}N_1$ M_0
	T_2 N_2 M_0		
	T_2 N_2b M_0		

TABLE 11:ASSOCIATION OF TNM STAGE WITH MARGIN OF THE GLANDS

GLAND	GROUP	MARGIN		P VALUE
		REGULAR(n%)	IRREGULAR(n%)	
RIGHT PAROTID	I	2(16.7%)	10(83%)	0.5
	II	1(9.1%)	10(90.9%)	
	III	0(0%)	7(100%)	
LEFT PAROTID	I	0	12(100%)	1
	II	0	11(100%)	
	III	0	7(100%)	
RIGHT SUBMANDIBULAR	I	8(66.7%)	4(33.3%)	0.338
	II	4(36.4%)	7(63.3%)	
	III	4(57.1%)	3(42.9%)	
LEFT SUBMANDIBULAR	I	8(66.7%)	4(33.3%)	0.947
	II	8(72.7%)	3(27.3%)	
	III	3(42.9%)	4(57.1%)	

TABLE 12: ASSOCIATION OF TNM STAGE WITH ECHOTEXTURE OF THE GLANDS

GLAND	GROUP	ECHOTEXTURE		P VALUE
		HOMOGENOUS (n%)	HETEROGENOUS (n%)	
RIGHT PAROTID	I	1(8.3%)	11(91.7%)	0.5
	II	0(0%)	11(100%)	
	III	1(14.3%)	6(85.7%)	
LEFT PAROTID	I	2(16.7%)	10(83.3%)	0,31
	II	3(27.3%)	8(72.7%)	
	III	0(0%)	7(100%)	
RIGHT SUBMANDIBULAR	I	2(18.2%)	10(83.3%)	0.977
	II	2(36.4%)	9(81.8%)	
	III	1(14.3%)	6(85.7%)	
LEFT SUBMANDIBULAR	I	4(33.3%)	8(66.7%)	0.947
	II	3(27.3%)	8(72.7%)	
	III	2(28.6%)	5(71.4%)	

TABLE 13: ASSOCIATION OF TNM STAGE WITH ECHOGENICITY OF THE GLANDS

GLAND	GROUP	ECHOGENICITY			P VALUE
		HYPERECHOIC	ISOECHOIC	HYPOECHOIC	
RIGHT PAROTID	I	0	2(16.7%)	10(83.3%)	0.6
	II	0	1(9.1%)	10(90.9%)	
	III	0	2(28.6%)	5(71.4%)	
LEFT PAROTID	I	0	2(16.7%)	10(83.3%)	0.74
	II	0	3(27.3%)	8(72.7%)	
	III	0	1(14.3%)	6(85.7%)	
RIGHT SUBMANDIBULAR	I	5(41.7%)	5(41.7%)	2(16.7%)	0.60
	II	7(63.6%)	2(18.2%)	2(18.2%)	
	III	2(28.6%)	3(42.9%)	2(28.6%)	
LEFT SUBMANDIBULAR	I	1(8.3%)	2(16.7%)	9(75%)	0.62
	II	2(18.2%)	3(27.3%)	6(54.5%)	
	III	0(0%)	1(14.3%)	6(85.7%)	

TABLE 14: ASSOCIATION OF TNM STAGE WITH VASCULARITY OF THE GLANDS

GLAND	GROUP	VASCULARITY		P VALUE
		INCREASE(n%)	DECREASE(n%)	
RIGHT PAROTID	I	10(83.3%)	2(16.7%)	0.09
	II	10(90.9%)	1(9.1%)	
	III	2(28.6%)	5(71.4%)	
LEFT PAROTID	I	6(50.0%)	6(50.0%)	0.80
	II	7(63.6%)	4(36.4%)	
	III	7(100.0%)	0(0%)	
RIGHT SUBMANDIBULAR	I	11(91.7%)	1(8.3%)	0.189
	II	9(81.8%)	2(18.2%)	
	III	4(57.1%)	3(42.9%)	
LEFT SUBMANDIBULAR	I	10(83.3%)	2(16.7%)	0.561
	II	7(63.6%)	4(36.4%)	
	III	5(71.4%)	2(28.6%)	

TABLE 15: COMPARISION OF TNM STAGING WITH PAROTID AND SUBMANDIBULAR GLANDS DIMENSIONS:

GLAND	PARAMETERS	STAGE	GROUP I	GROUP II	GROUP III	P VALUE
RIGHT PAROTID	Length	I	3.5±0.4	3±0.6	3.3±0.2	0.08
		II	2.7±0.5	2.3±0.7	2.4±0.3	0.23
	Width	I	2±0.7	1.6±0.6	1.9±0.6	0.36
		II	1.1±0.2	1.1±0.3	1.3±0.3	0.29
	Depth	I	2.1±0.4	2.0±0.7	1.4±0.6	0.06
		II	1.4±0.2	1.5±0.5	1.1±0.3	0.11
LEFT PAROTID	Length	I	3.4±0.4	3.1±0.6	3.1±0.6	0.39
		II	4.8±6.3	2.4±0.6	2.4±0.6	0.35
	Width	I	1.7±0.7	1.4±0.8	1.4±0.2	0.6
		II	1.3±0.5	1.1±0.4	1.2±0.4	0.23
	Depth	I	1.8±0.5	1.8±0.7	1.3±0.4	0.13
RIGHT SUBMANDIBULAR		II	1.4±0.4	1.3±0.5	1.1±0.2	0.35
	Length	I	3.6±0.2	3.0±0.3	2.9±0.4	0.70
		II	2.4±0.2	2.1±0.4	2.2±0.3	0.35
	Width	I	1.3±0.3	1.3±0.3	1.4±0.5	0.69
		II	1.1±0.2	1.1±0.2	1.0±0.2	0.76
	Depth	I	1.7±0.4	1.8±0.8	1.2±0.2	0.12
		II	1.3±0.4	1.3±0.4	1.0±0.4	0.35
LEFT SUBMANDIBULAR	Length	I	3.0±0.2	2.9±0.3	2.9±0.4	0.7
		II	2.5±0.3	2.5±0.2	2.3±0.4	0.53
	Width	I	1.3±0.3	1.2±0.3	1.5±0.3	0.311
		II	1.1±0.2	0.9±0.1	2.9±5.0	0.207
	Depth	I	1.8±1.0	1.5±0.5	1.4±0.4	0.635
		II	1.2±0.1	1.0±0.2	1.1±0.4	0.270

FIG 1: SEX DISTRIBUTION

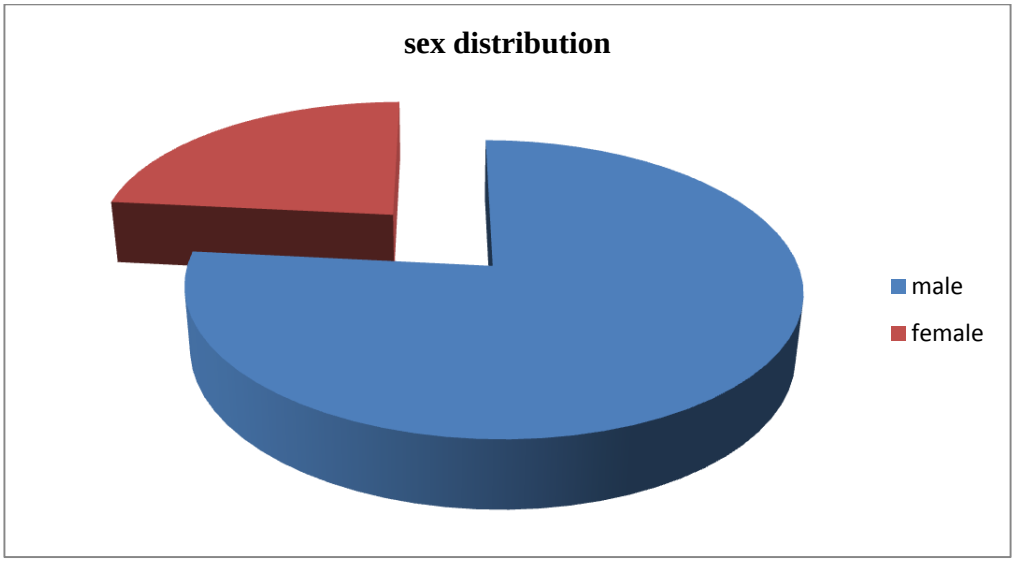


FIG: 2 GRAPHICAL REPRESENTATION OF TNM STAGING

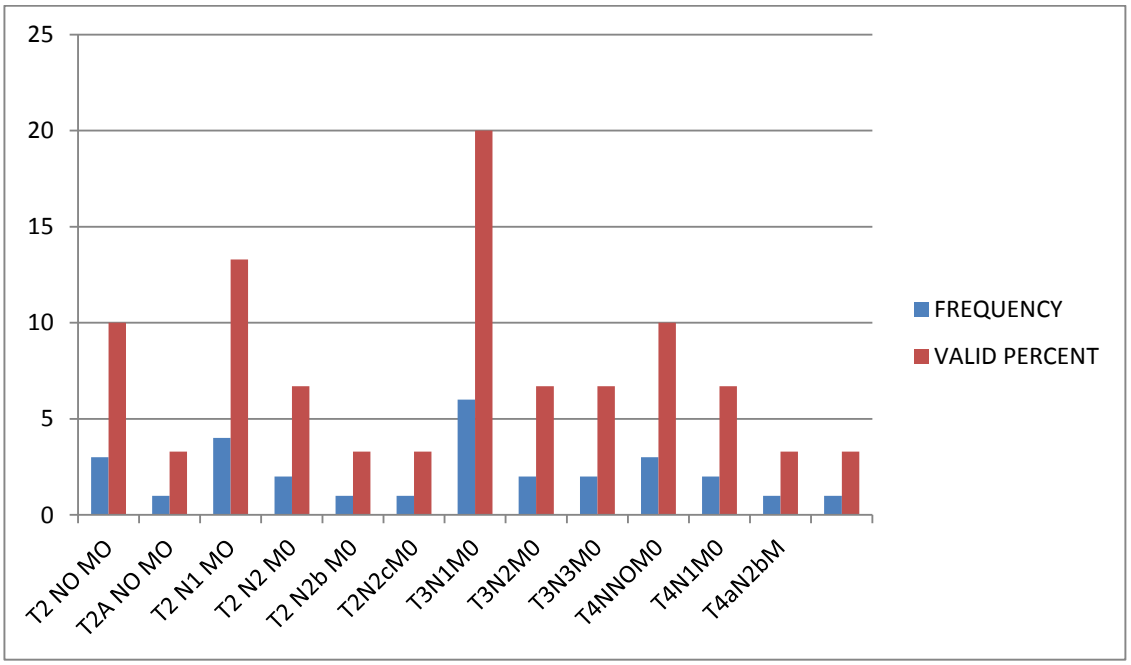
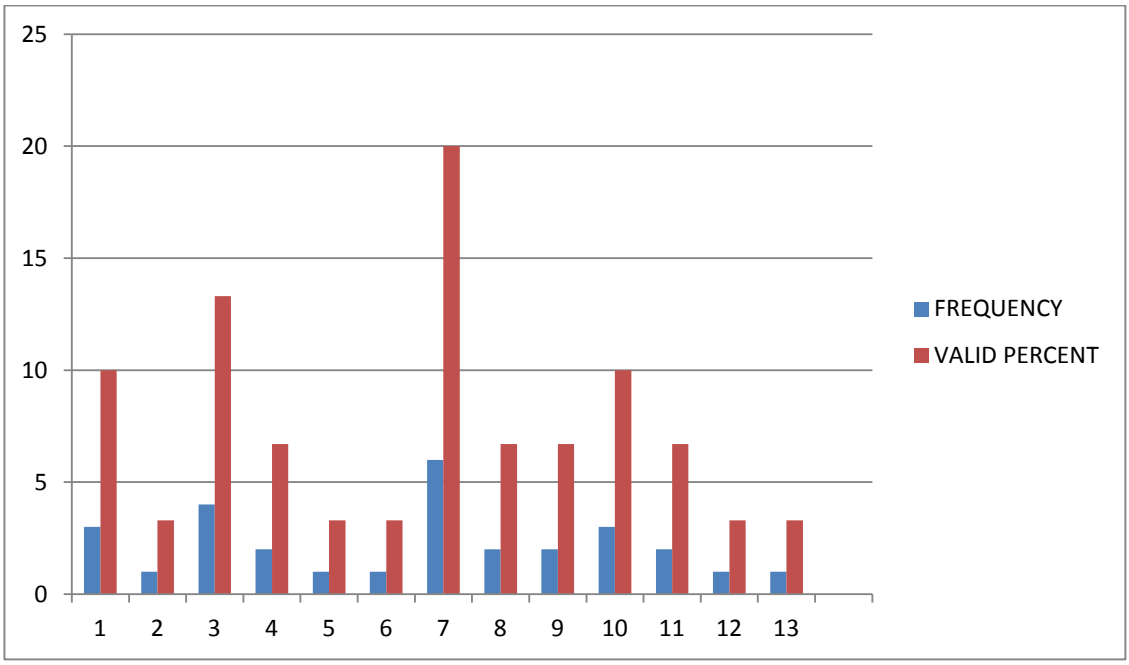


FIG: 3 GRAPHICAL REPRESENTATION OF SITE & FREQUENCY



1 .Right buccal mucosa

2. Left buccal mucosa

3. Anterior 2/3rd of tongue

4. Right Lateral Surface of Tongue

5. Floor of the mouth

6. Right side upper Alveolus/ Hard Palate

7. Rightt Buccal Mucosa and Floor of Mouth

8. Anterior 2/3rd of tongue and Floor of the mouth

9. Right buccal mucosa and right Alveolus

10. Left buccal mucosa and Retromolar trigone

11. Left side upper alveolus and hard palate and Retromolar trigone

DISCUSSION

Sonography is a safe and valuable technique for monitoring the changes in salivary glands caused by radiotherapy and provides important information regarding the morphologic changes of the glands.[24] This study showed several changes of parotid and submandibular salivary glands when evaluated in two stages, before radiotherapy and six weeks after completion of radiotherapy.

During examination we observed decrease in overall size of salivary glands, following radiotherapy. There was decrease in length, width and depth of both the parotid and submandibular salivary glands. chronic inflammation which occurs in the salivary glands after exposure to radiation leads to acinar cell loss and acinar atrophy[71] causes fibrous changes in the glands which subsequently leads to decrease the overall size of both parotid and submandibular glands. This study showed statistically significant results for all values. This changes were different in other organs changes those occur following radiotherapy. Radiotherapy causes inflammation, swelling and hyperthermia which leads to increase the organ size. In previous studies[72] and Wada et al.2009 conducted a study on changes of salivary glands using MRI found similar results of our evaluation. Price et al reported significant loss of serous and mucous acini in the submandibular glands following radiation exposure over 50 Gy[73] documented a study on Hanford mini pigs and found following one month after irradiation causes parenchymal loss and acinar atrophy that leads to shrinkage of the submandibular salivary glands. Barker et al.2004 and lee et al.2008 documented radiation induced volume reduction of parotid gland by using CT.

Burke et al, Orloff et al,[74] also reported similar results. Ying et al.[47] reported only a significant difference concerning the width of the parotid glands. Eva et al reported that the

size of salivary glands changes only in acute situations, while in chronic conditions the size decreases due to the atrophy. Also stated that the reduction in size of the gland may be a end result of acinar atrophy and parenchymal damage. Grehn et al.[75] stated that the loss of acinar cells was dose dependent, higher radiation dose causes greater cell loss leading to loss of volume of the glands. S C H Cheng et al.[48], assessed post radiotherapy changes in parotid glands and observed dimension changes in parotid and submandibular glands. Our study results were similar to Imanimognaddam et al.[24] who evaluated changes in parotid and submandibular glands 2 weeks and 6 weeks following radiotherapy and observed significant reduction in dimensions of glands. Dr Rithiga gindal et al.[49] did a similar study, ultrasonographic evaluation of salivary glands before radiotherapy and after completion of radiotherapy and we found the results similar to ours.

In this study we qualitatively evaluated margin, echotexture, ecogenicity,and vascularity of both right and left parotid & submandibular glands before radiotherapy and six weeks after completion of radiotherapy. We observed a change in margin, from regular, to irregular, echotexture from homogenous to heterogenous, echogenicity from hyperechoic to isoechoic or hypoechoic six weeks after radiotherapy.

The ultrasound evaluation of salivary glands of 30 oral cancer patients revealed regular margins before radiotherapy, 90% patients showed irregular margin on evaluation of right parotid, 100% patients showed irregular margin on evaluation of left parotid, 46.7% patients showed irregular margins on evaluation of right submandibular gland, 36.7% patients showed irregular margin on evaluation of left submandibular gland six weeks after completion of radiotherapy. The result showed statistically significant change of margins from regular to

irregular may be due to parenchymal loss or acinar atrophy. These results were similar to the previous studies conducted by Imanimognaddam et al[24], Dr Rithiga gindal et al[49].

Like in the previous studies echogenicity of parotid glands were compared with adjacent masseter muscle. Ying et al.[47] stated that the radiation tolerance of muscle was found significantly higher that of parotid gland and hence the echogenicity variation of muscle after irradiation should not be as much as that in parotid glands. In our study 16.7% patients showed isoechoic and 83.3% patients showed hypoechoic right parotid ,20% patients showed isoechoic and 80% patients showed hypoechoic left parotid,33.3% patients showed isoechoic, and 20% of patients showed hypoechoic right submandibular.20% patients showed isoechoic, 70% hypoechoic and 10% showed hyperechoic echogenicity in left submandibular salivary glands. On the whole salivary glands echogenicity significantly changed from hyperechoic to hypoechoic after radiotherapy may be due to inflammatory infiltration and fibrosis of the glands. These inflammatory infiltrate could lower the echogenicity in post radiotherapy glands.Radfar and sirosis.[73]

Seifert et al.[77];Teymoortash et al.2005 stated that radiation induced chronic sialadenitis had been reported in the salivary glands of post RT head and neck cancer patients characterized by inflammatory infiltration and fibrosis histopathologically.

In his study ying et al.2007[47] found that the hypoechoic inflammatory infiltrate could lower the echogenicity of the parotid glands, leading to decreased echogenicity in post-RT glands. Price et al.1995[77] stated that the decreased echogenicity in post radiotherapy parotid gland was probably due to reduced refractive interfaces for ultrasound beam because of the loss of secretory granules and acinar cells after irradiation. S C H Cheng et al[48], assessed post

radiotherapy changes in parotid and submandibular glands and observed echogenicity changed from hyperechoic to isoechoic and hypoechoic on ultasonographic evaluation .Our study results were similar to Imanimognaddam et al (2012)[24] who evaluated changes in parotid and submandibular glands two weeks and six weeks following radiotherapy and observed significant reduction in dimensions of glands. On ultrasound he found glandular texture became heterogenic, hypoechoeic and irregular following radiation exposure.

In our study on ultrasound evaluation 100% patients showed homogenous echotexture of both parotid and submandibular salivary glands before radiotherapy.93.3% patients showed heterogenous on evaluation of right parotid, 100% patients showed heterogenous echotexture on evaluation of left parotid,83.3% patients showed heterogenous echotexture on evaluation of right submandibular gland, and 100% patients showed heterogenous echotexture on evaluation of left submandibular gland six weeks after radiotherapy..This change is due to parenchymal loss and acinar atrophy in irradiated glands leading to non uniform ultrasound interfaces.

Grehn et l.(1997),[75]and ying et al.(2007)[47] reported that on ultrasound evaluation of parotid and submandibular salivary gland showed homogenous echotexture before radiotherapy, where as salivary glands in the patients treated with conventional RT were predominately heterogenous. The heterogenous echo pattern of the parotid gland was due to the presence of non uniform ultrasound interfaces from the disorganized acinar cell arrangement after parenchymal loss and acinar atrophy in high dose irradiated glands. They also stated that the presence of patches of inflammatory infiltrates due to radiation induced chronic sialadenitis would appear multiple hypoechoic areas within the gland, leading to heterogenous echopattern. Our study results were similar to the previous studies conducted by

yang et al.(2007)[47] , S C H Cheng et al.(2011)[48], Imanimognaddam et al (2012)[24], Dr Rithiga gindal et al (2015)[49].

On color Doppler we observed decrease in vascularity qualitatively six weeks after radiotheraphy but not considered as statistically significant. The overall decrease is because of destruction of glandular parenchyma secondary to radiation exposure there will be decrease resistance to blood flow initially but later because of both acinar, parenchymal destruction and endarteritis there will be decrease in blood flow in glandular tissue. In previous studies, S C H Cheng et al. (2011)[48], Imanimognaddam et al (2012)[24], Dr Rithiga gindal et al (2015)[49], authors did quantitative assessment of blood flow and velocity. We couldn't find any published data regarding the qualitative assessment of vascularity of the glands.

In this study various TNM stages were grouped in to three groups based on the size of the tumor (T2-Group I, T3-Group II, T4-Group III) and compared with ultrasonographically evaluated post radiotherapy salivary gland changes. We found that the changes in the quantitative parameters of the salivary glands of both the parotid and submandibular salivary glands in between the groups were insignificant. In addition to quantitative parameters, qualitative parameters including margin, echotexture, echogenicity, vascularity were also compared, and we found that there was no statistically difference present in intergroup comparison. Results showed no significant difference between the groups which denotes that the changes in the salivary glands evaluated by ultrasound were due to effect of radiation irrespective of the tumor size.

Saliva changes:

Few reports in the literature address the status of salivary pH after irradiation, especially that of whole saliva. The published data do indicate however, that irradiation to salivary gland appears to cause a slight decrease in the pH even in long term follow up studies. The present study has revealed that the mean pH for all patients had significantly reduced from mean value 6.5±0.5 to mean value 5.2±0.4 six weeks after completion of radiation. This pH is low enough to initiate decalcification of normal enamel. For pH This observation is consistent with the reports of Dreizen et al (1976)[54].

In this present study salivary sodium level significantly increased, mean value 43.7±12.1 after radiotherapy when compared to pre radiotherapy values ,mean value 19.5±6.And potassium level significantly reduced from pre radiotherapy mean value18.4±5 to post radiotheraphy mean value 16.9±5.1.The increased sodium and reduction of potassium maybe due to reduced flow rate of saliva & xerostomia induced and reflects the radiation damage to both the acinar and ductal systems.

An increase in the concentrations of sodium, calcium, and magnesium has been reported, while the concentration of potassium is only slightly affected Dreizen *et al.*[54] (oral sequelae)

The increase in the salivary calcium reflects the reduced fluid output of the acinar cells and resulting in the concentration of acinar products. The present study revealed that the mean level of salivary calcium in all the patients had increased after 6 weeks of radiation 4.7±1.1, when compared to the pre radiation mean value 3.6±0.8.

Of the components studied, amylase originates from the salivary glands and thus serves as an indicator of the protein synthesis in the acinar cells. Makkonen T.A. et al in 1986[60] reported that in addition to the flow rate measurements amylase seems to be the best indicator of salivary gland function during radiotherapy. The present study revealed that there was a marked reduction in the mean salivary amylase level 46.2±102.6 when compared to the pre radiation mean value 310±174.1.

The mean value of the total protein for all patients increased from mean value 1.5±0.3 to 1.8±0.3after 6 weeks during radiotherapy, when compared to the mean value before radiation. The increase in protein after radiotherapy reflects the radiation effect resulting acinar destruction.The finding of the marked reduction in the level of salivary amylase and increase the level of total protein was consistent with observations of Makkonen T.A et al[60].

CONCLUSION:

A total of 30 oral cancer patients who fulfilled the inclusion and exclusion criteria were selected for this study. Among the 30 patients 23 were males and 7 females. Age range of the patient was 30-70. All planned for conventional radiation treatment with cobalt 60 apparatus in the department of radiation Oncology, RGGGH, Chennai for carcinoma of the oral cavity. Field of RT unilateral or bilateral. The treatment planned for 5 days in a week. The weekly dosage was 10 Gy (gray). The total dosage given varied from 60 to 66 Gy and administered over a period of 6 to 7 weeks. Ultrasonographic evaluation of 60 parotids and 60 submandibular glands were done prior to radiotherapy and six weeks after completion of radiotherapy to evaluate the length, width, depth, echotexture, echogenicity, and vascularity of salivary glands and unstimulated whole saliva was collected before and after radiotherapy for analsis the levels of salivary pH,Na,K,Ca,amylase,and total protein.

We found that that length, width and depth of parotid and submandibular glands significantly reduce after radiotherapy.Also, margins, echotexture, echogenicity of the gland s Changes in to irregular, heterogenic,and hypoechoic respectively due to to the acini changes and presence of inflammatory processes.comparision of TNMstaging of the tumor based on size with post radiotherapy changes of the salivary glands also done which showed insignificant results. This denotes salivary gland changes were only dependent on radiation irrespective of the size of the tumor. We also concluded that salivary sodium,calcium and total protein level increases after radiotherapy and salivary PH K,and amylase significantly reduces after radiotheraphy. These changes can be due to parenchymal damage and acinar loss in the glands due to radiation.

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26-09-2015

Ref No: R.C No.0430/DE/2015 dated 27.01.2015, O/O Principal, TNGDC
Sub: IEC review of the research proposals,

Title of the work: Ultrasonographic analysis of salivary glands and Biochemical analysis of whole saliva in pre and post radiotherapy oral cancer patients

Principal Investigator: Dr.R. Vasudevi.
II Yr. M.D.S., Student.

Department : Department of Oral Medicine and Radiology
Tamil Nadu Govt. Dental College & Hospital , Chennai-3

Thank you for submitting your research proposal , which was considered at the Institutional Ethics Committee meeting held on 02-07-2015, at TN Govt. Dental College and the documents related to the study referred above were discussed and the modifications done as suggested and reported to us through your letter dated 25-09-2015 have been reviewed.

The decision of the members of the committee , the secretary and the Chairperson IEC of TN Govt. Dental College is here under:

Approved	Approved and advised to proceed with the study
Approved with suggestions	----------
Revision	----------
Rejected	----------

The principal investigators and their team are advised to adhere the guide lines given below:

1. You should get detailed informed consent from the patients / participants and maintain confidentiality.
2. You should carry out the work without affecting regular work and without extra expenditure to the Institution or the Government.
3. You should inform the IEC, in case of any change of study procedure, site, and investigating guide.
4. You should not deviate from the area of work for which you have applied for ethical clearance.
5. You should inform the IEC immediately in case of any adverse events or serious adverse reactions. You should abide to the rules and regulations of the institution(s) .
6. You should complete the work within specific period and if any extension of time is required, you should apply for permission again to do the work.
7. You should submit the summary of the work to the ethical committee every 3 months and on completion of the work.
8. You should not claim any kind of funds from the institution for doing the work or on completion/ or for any kind of compensations.
9. The members of the IEC have the right to monitor the work without prior intimation.
10. Your work should be carried out under the direct supervision of the guide/ Professor.

MEMBER SECRETARY,
INSTITUTIONAL ETHICS COMMITTEE
Tamil Nadu Govt. Dental College & Hospital
Chennai

CHAIRPERSON
INSTITUTIONAL ETHICS COMMITTEE
Tamil Nadu Govt. Dental College & Hospital
Chennai

From

Dr.S.Jayachandran MDS,Phd, MAMS.
Prof. and Head of Department
Department of Oral Medicine and Radiology
Tamil Nadu Government Dental College & Hospital
Chennai – 600 003.

To

The Director
Barnard Institute of Radiology & oncology.
Rajiv Gandhi Government General Hospital
Chennai – 600 003.

Sub: Reg. permission to utilize the facility for dissertation work

Sir/Madam

I hereby inform, a bonafide student Dr.R.Vasudevi II year Post graduate, Department of oral medicine and radiology TNGDCH, Chennai is doing dissertation on "Ultrasonographic analysis of salivary glands and biochemical analysis of whole saliva in pre and post radiotherapy oral cancer patients" which got approval from Institutional Ethics committee. Kindly permit her to utilize the facility available in radiology and oncology department to complete her dissertation work. Kindly do the needful.

Thanking you

Date : 28/10/15

Place : Chennai

Yours faithfully

S/Jayachandran
28/10/15

Dr. S. JAYACHANDRAN, MDS., Ph.D.,
Professor & Head,
Dept. Of Oral Medicine & Radiology,
Tamilnadu Govt. Dental College & Hospital,
Chennai-600 003

To see Dr. Vasanthi
6/11/15

2/11/15

PARTICIPATION INFORMATION SHEET

STUDY TITLE: "**Ultrasonographic analysis of salivary glands and Biochemical analysis of whole saliva in pre and post radiotherapy oral cancer patients** " .

Name of the Research Instituition:

1. TamilNadu Government Dental College & Hospital, chennai-03.
2. Barnard Institute of Radiology, RGGGH, Chennai- 01
3. Department of Biochemistry,RGGGH,Chennai-01

1. Purpose of the study:

   To analyse ultrasonographic changes in parotid and submandibular salivary glands in oral cancer patients before and after radiotherapy and biochemical changes of the saliva at the same time

Procedures :

1. Patient selection.
2. Obtaining thorough history and informed consent.
3. Complete Clinical Examination (intra and extra oral examination) by using diagnostic instrument set.
4. Ultrasound analysis of Parotid and Submandibular salivary glands is carried out before and after radiotherapy in oral cancer patients.
5. About 5ml/ table spoon quantity of Patients saliva of same patients
   a. is collected in a sterile container before and after radiotherapy and
   b. subjected to biochemical analysis .

3 Risk of participation :

Patients are selected only by proper inclusion and exclusion criteria so ,as the procedure is non –invasive the risk of participation is negligible .collection of saliva is safe and quicker **,** thus sample collection is harmless to the patient.

4. Benefits :

Patients will be benefited by early diagnosis of saliva and salivary gland changes by a non- invasive procedure.

5. Confidentiality **:**

The identity of the patients participating in the research will be kept confidential throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

6. Participant's rights:

a).Taking part in the study is voluntary. You are free to decide whether to participate in the study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

b).The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

1. Outcome of the study: This study helps to observe salivary gland &saliva changes before and after radiotherapy and further helps the timely management of xerostomia related oral disorders in patients who are participating.

7 .Compensation**:** Nil

8. Contacts for queries related to the study:

Primary Investigator name: Dr.R.Vasudevi.

Contact details :Department of Oral Medicine ad Radiology,

Tamil Nadu government Dental college and Hospital,

Frazer Bridge Road

Chennai-600003

Phone number : 9677704650

(For queries related to the rights as a study participant, please write to: The Chairperson, IEC-TamilNadu government dental college and Hospital,Chennai-600003)

ஆராய்ச்சி பற்றிய தகவல் படிவம்

கதிரியக்க சிகிச்சை பெறப்போகும் வாய்புற்று நோயாளிகளின் உமிழ்நீர் சுரப்பி பற்றிய திறனாய்வு மற்றும் உமிழ்நீரின் உயிர்வேதியியல் மாற்றங்கள் குறித்த ஆய்வு கதிரியக்க சிகிச்சைக்கு முன் மற்றும் பின்.

நோயாளிகள் பற்றிய குறிப்புகள் ஆராய்ச்சி முடியும் வரை ரகசியமாக பாதுகாக்கப்படும். இந்த ஆராய்ச்சியை வெளியிடும்போது நோயாளிகளின் தனிப்பட்ட விவரங்கள் எதுவும் பாதிக்கப்படமாட்டாது.

இந்த ஆராய்ச்சியில் பங்குபெறுவது நோயாளிகளின் தனிப்பட்ட விருப்பம். மேலும் நோயாளிகள் இந்த ஆராய்ச்சியிலிருந்து எப்போது வேண்டுமானாலும் விலகிக்கொள்ளலாம். நோயாளியின் இந்த முடிவினால் அவருக்கோ அல்லது ஆராய்ச்சியாளருக்கோ எந்தவித பாதிப்பும் கிடையாது.

இந்த ஆராய்ச்சியின் முடிவுகள் நோயாளிகளுக்கு ஆராய்ச்சியின் இடையிலோ அல்லது முடிவிலோ தெரிவிக்கப்படும். இதில் ஏதேனும், பின் விளைவுகள் ஏற்பட்டால் அதை சரிசெய்ய சிகிச்சையளிக்க தகுந்த உதவிகள் செய்யப்படும்.

ஆய்வாளரின் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

தேதி :

இடம் :

Annexure: AF 06/004/01.0

Template for Informed Consent Form

Informed Consent Form "ULTRASONOGRAPHIC ANALYSIS OF SALIVARY GLANDS AND BIOCHEMICAL ANALYSIS OF WHOLE SALIVA IN PRE AND POST RADIOTHERAPY ORAL CANCER PATIENTS "

Participant ID No:

"I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study and understand that I have the right to withdraw from the study at any time without in any way it affecting my further medical care."

Date Name of the participant Signature/thumb impression of the participant

[The literate witness selected by the participant must sign the informed consent form. The witness should not have any relationship with the research team; If the participant doesn't want to disclose his / her participation details to others, in view of respecting the wishes of the participant, he / she can be allowed to waive from the witness procedure (This is applicable to literate participant ONLY). This should be documented by the study staff by getting signature from the prospective participant]

_____

_____

"I have witnessed the accurate reading of the consent form to the potential participant and the individual has had opportunity to ask questions. I confirm that the individual has given consent freely"

_____

Date Name of the witness Signature of the witness

_____

Date Name of the interviewer Signature of the interviewer

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

கதிரியக்க சிகிச்சை பெறப்போகும் வாய்புற்று நோயாளிகளின் உமிழ்நீர் சுரப்பி பற்றிய திறனாய்வு மற்றும் உமிழ்நீரின் உயிர்வேதியியல் மாற்றங்கள் குறித்த ஆய்வு கதிரியக்க சிகிச்சைக்கு முன் மற்றும் பின்.

ஆராய்ச்சி நிலையம் : அரசு பல் மருத்துவக் கல்லூரி
சென்னை

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் எண் :

பங்கு பெறுபவரின் பிறந்த தேதி : ..... / ..... / .....
தேதி மாதம் வருடம்

இந்த ஆய்வு சம்பந்தமாக நான் மேலே கூறப்பட்ட தகவல் படிவத்தை முழுமையாக படித்துப் பார்த்தேன் என்று உறுதி கூறுகிறேன்.

நான் இது தொடர்பான அனைத்து கேள்விகளுக்கும் நிறைவான பதில்கள் பெறப்பட்டேன்.

இந்த ஆய்வின் எனது பங்கு தன்னிச்சையானது என்றும் எந்த நேரத்திலும் இந்த ஆய்வில் இருந்து சட்ட உரிமைகள் பாதிக்கப்படாமல் விலகிக் கொள்ள சம்மதிக்கிறேன்.

மருத்துவ ஆய்வு அதிகாரிகள், எனது சிகிச்சை தொடர்பான பதிவேடுகளை பார்வையிடவும் எந்த நேரத்திலும், ஆய்வில் இருந்து நான் விலகினாலும் பார்வையிட சம்மதிக்கிறேன். எனது அடையாள குறிப்புகள் மூன்றாவது நபருக்கு தெரிவிக்கப்படமாட்டாது என்று புரிந்து கொண்டேன்.

இந்த ஆய்வு அறிக்கைகளை பயன்படுத்தவும், வெளியிடவும், நான் சம்மதிக்கிறேன். ஆய்வாளர் எனது மருத்துவக் குறிப்புகளை வெளியிட தடையாக இருக்கமாட்டேன் என உண்மையாக சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி .....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி .....

ஆய்வாளரின் பெயர் .....

DEPARTMENT OF ORAL MEDICINE AND RADIOLOGY

TAMIL NADU GOVT. DENTAL COLLEGE & HOSPITAL, CHENNAI -3

CASE PROFORMA

Ultrasonographic analysis of salivary glands and Biochemical analysis of whole saliva in pre and post radiotherapy oralcancer patients.

Date: Serial no:

Name: O.P No:

Age/Sex:

Permanent address

Temporary Address

Phone no:

Occupation: Income:

Religion:

District :

State :

Pathology report

Center :

Centre: Department of Oral Medicine And Radiology,

Tamil Nadu Govt Dental College & Hospital, Chennai -3

Ref. No &Date:

Nature of Biopsy:

CASE HISTORY

Presenting complaint with duration:

History of present illness and treatment,if any:

Previous illness and treatment:

Personal history and habits

- Frequency :

A) Smoking habit:
   - Material used:
   - Frequency :
   - Duration of the habit:

B) Chewing habit:
   - Material used:
   - Frequency :
   - Duration of the habit:

C) Other habits (alcohol, snuff):

Family history:

CLINICAL EXAMINATION

Extraoral Examination:

Intraoral examination:

- Teeth:
- Gingiva:
- Labial and buccal mucosa:
- Hard palate:
- Soft Palate:
- Pillar of fauces and Tonsils:
- Tongue:
- Floor of the mouth:
- Retromolartrigone:

Description of the primary lesion:

Description of the secondary nodes:

Distant metastasis:

TNM staging:

Provisional diagnosis:

Investigations:

1. Laboratory investigations:
    A. Blood:
        RBC Count:
        WBC count:
        Total count: Erythrocyte sedimentation rate:
        Differential count:
        Bleeding time:
        Haemoglobin %:
        Clotting time:
        Peripheral smear:
    B. Urine:
        Glucose:

c) Saliva Biochemical Readings:

S.NO		Pre radiotherapy	Post radiotheraphy
1	Na		
2	K		
3	Ca		
4	PH		
5	Salivary amylase		
6	Salivary protein		

OTHERS:

1) ULTRASONOGRAPHIC EVALUATION OF SALIVARY GLANDS :

PRE RADIOTHERAPHY

Study parameters	Parotid		Submandibular	
Size(legth,width,depth)				
Ecogenicity				
Ecotexture				
Margins				
Vascularity				

POST RADIOTHERAPHY

Study parameters	Parotid		Submandibular	
Size(length,width,depth)				
Ecogenicity				
Ecotexture				
Margins				
Vascularity				

Clinical diagnosis:

Treatment plan:

TRIPARTITE AGREEMENT

This agreement herein after the "Agreement" is entered into on this day ----------between the Tamil Nadu Government Dental College and Hospital represented by its **Principal** having address at Tamil Nadu Government Dental College and Hospital, Chennai – 600 003, (hereafter referred to as, 'the college')

And

Prof Dr.S.JAYACHANDRAN,M.D.S.,Ph.D., aged 52 years working as **Professor** in Department of Oral Medicine and Radiology at the Tamil Nadu Government Dental College, having residence address at A.M-16,TNHB quarters ,tod hunter nagar,Saidapet, Chennai -600015 (Herein after referred to as 'Principal Investigator')

And **Dr.R.VASUDEVI** aged 36 years currently studying as **Post Graduate student** in Department of Oral Medicine and Radiology, Tamil Nadu Government Dental College, residing at No.23,A2,second floor, Swami reddy street,Egmore.Chennai-600008 (herein after referred to as the 'PG and co- Investigator').

Whereas the PG student as part of her curriculum undertakes this research on "**ULTRASONOGRAPHIC ANALYSIS OF SALIVARY GLANDS AND BIOCHEMICAL ANALYSIS OF WHOLE SALIVA IN PRE AND POST RADIOTHERAPHY ORAL CANCER PATIENTS"** for which purpose the Guide shall act as Principal investigator and the college shall provide the requisite infrastructure based on availability and also provide facility to the PG student as to the extent possible as a Co- investigator.

Whereas the parties, by this agreement have mutually agreed to the various issues including in particular the copyright and confidentiality issues that arise in this regard.

Now this agreement witnessed as follows

1. The parties agree that all the Research material and ownership therein shall become the vested right of the college, including in particular all the copyright in the literature including the study, research and all other related papers.
2. To the extent that the college has the legal right to do go, shall grant to licence or assign the copyright so vested with it for medical and/or commercial usage of interested persons/ entities subject to a reasonable terms/ conditions including royalty as deemed by the college.
3. The royalty so received by the college shall be shared equally by all the three parties.
4. The Co-investigator and Principal Investigator shall under no circumstances deal with the copyright, Confidential information and know

– how – generated during the course of research/study in any manner whatsoever, while shall sole west with the college.

5. The Co-investigator and Principal Investigator undertake not to divulge (or) cause to be divulged any of the Confidential information or, know – how to anyone in any manner whatsoever and for any purpose without the express written consent of the college.
6. All expenses pertaining to the research shall be decided upon by the Principal investigator/ Co-investigator or borne sole by the PG student (Co-investigator)
7. The college shall provide all infrastructure and access facilities within and in other institutes to the extent possible. This includes patient interactions, introductory letters, recommendation letters and such other acts requires in this regard.
8. The Principal Investigator shall suitably guide Co-investigator the Student Right from selection of the Research Topic and Area till its completion. However the selection and conduct of research, topic and area of research by the student researcher under guidance from the Co-Investigator shall be subject to the prior approval, recommendations and comments of the Ethical Committee of the College constituted for the purpose.
9. It is agreed that as regards other aspects not covered under this agreement, but which pertain to the research undertaken by the Co-investigator, under the guidance from the Principal Investigator, the decision of the college may be binding and final.
10. If any dispute arises as to the matters related or connected to this agreement herein, it shall be referred to arbitration in accordance with the provisions of the Arbitration and Conciliation Act, 1996.

In witness whereof the parties hereinabove mentioned have on this day month and year herein above mentioned set their hands to this agreement in the presence of the following two witnesses.

College represented by its **Principal** **PG Student**

Witnesses **Student Guide**

1.

2.

S.NO	DATE	PIN NO	NAME	AGE	SEX	SITE	DOSE	FO RT	STAGE	TNM STAGE
1	15/06/2015	92558	Veerappan	40	Male	ant2/3 rd tongue	66	bilateral	T3N3M0	2
2	2/-06/2015	96593	Pappammal	64	Female	(Rt)BM	60	unilateral	T4N0M0	3
3	14/11/2015	145544	Maria john	60	Male	(Rt)LS T	66	bilateral	T2N0M0	1
4	11/12/2015	187641	Sargunan	42	Male	ant2/3 rd T	66	bilateral	T4aN0M0	3
5	13/12/2015	169804	Antony	47	Male	(Rt)BM	60	unilateral	T2N2cM0	2
6	18/12/2015	165802	Uthiramary	65	Female	(Rt)BM	60	unilateral	T3N1M0	2
7	17/12/2015	186701	Elumalai	59	Male	(Rt)max.alveolus&HP	66	bilateral	T2N0M0	1
8	28/12/2015	484412	Subbaiya	60	Male	ant2/3 rd T	66	bilateral	T4bN1M0	3
9	15/02/2016	188860	Saravanan	42	Male	(Rt)BM	60	unilateral	T2N1M0	1
10	18/02/2016	190381	Rosyammal	60	Female	ca(Lt)BM	60	unilateral	T3N2aM0	2
11	19/02/2016	198507	Guruswamy	65	Male	(Lt)lower alveolus &RMT	66	bilateral	T3N1M0	2
12	24/02/2016	191783	Devi	30	Female	ant T2/3 &FOM	66	bilateral	T4N1M0	3
13	29/02/2016	194353	Pandurangan	60	Male	FOM	66	bilateral	T4N1M0	3
14	2/3/2016	193675	Karra Issac	60	Male	ant2/3 rd T	66	bilateral	T2N0M0	1
15	4/3/2016	197722	Kaliyammal	45	Female	(Rt)Lower alveolus	66	unilateral	T4aN0M0	2
16	5/3/2016	198105	Ganesh	38	Male	(Rt)BM	60	unilateral	T2N0M0	1
17	9/3/2016	198248	Saroja	70	Female	(Rt)BM&HT	66	bilateral	T3N1M0	2
18	14/03/2016	196852	Babu	39	Male	(Rt)BM&FOM	66	bilateral	T2N2bM0	1
19	18/03/2016	204701	Lakshmi	45	Female	T &FOM	66	bilateral	T3N2M0	2
20	21/03/2016	192645	Raja	62	Male	(Rt)up alveolus	60	unilateral	T3N1M0	2
21	21/03/2016	205680	Munusamy	42	Male	(Rt)lat.sf T	66	bilateral	T3N1M0	2
22	22/03/2016	204787	Tamilvanan	38	Male	(Lt)BM	60	unilateral	T2N0M0	1
23	4/4/2016	178507	Mariyaselvam	53	Male	(Rt)BM	60	unilateral	T2N1M0	1
24	19/04/2016	216352	Balakrishnan	45	Male	FOM	66	bilateral	T2N2M0	1
25	28/04/2016	223174	subramani	55	Male	ca(Lt)lower alveolus	60	unilateral	T2N2M0	1
26	6/6/2016	242548	Chinnadurai	35	Male	(Lt)BM&RMT	66	bilateral	T2N1M0	1
27	23/06/2016	247818	Pandian	54	Male	T &FOM	66	bilateral	T4aN2bM	3
28	21/07/2016	260984	Mani	55	Male	(Rt)BM&max. alveolus	66	unilateral	T4N0M0	3
29	3/8/2016	266708	Raja	51	Male	T(Rt)lat.sf	60	bilateral	T3N1M0	2
30	4/8/2016	266957	Kuppusamy	60	Male	T(Rt)lat.sf	60	bilateral	T2aN0M0	1

S.NO	NAME	RIGHT PAROTID GLAND PRE RADIOTHERAPY							LEFT PAROTID GLAND POST RADIOTHERAPY						
		L	W	D	M	ET	EG	V	L	W	D	M	ET	EG	V
1	Veerappan	3.3	1.7	1.6	0	1	1	1	2.7	0.8	1.2	1	2	3	1
2	Pappammal	3.6	2.4	0.7	0	1	1	1	2.24	2	0.7	1	2	3	1
3	Maria john	3.78	2.6	2.1	0	1	1	1	3.3	1.64	1.52	1	2	3	1
4	Sargunan	3.3	1.1	1.1	0	1	1	1	2.4	0.97	1	1	2	2	2
5	Antony	2.23	1.02	2.1	0	1	1	1	1.9	0.9	1.7	1	2	3	1
6	Uthiramary	4.19	1.94	3.28	0	1	1	1	3.29	1.09	2.5	1	2	3	1
7	Elumalai	3.8	3.2	1.8	0	1	1	1	2.9	1.25	1.2	0	2	3	1
8	Subbaiya	3.9	1.9	1.1	0	1	1	1	2.8	1.56	1	1	2	3	2
9	Saravanan	3.89	2.26	2.34	0	1	1	1	2.89	1.16	1.34	1	2	3	1
10	Rosyammal	3.7	3.1	2.9	0	1	1	1	2.8	2.2	2.1	1	2	3	2
11	Guruswamy	2.8	1.4	0.9	0	1	1	1	2.2	1.01	0.9	1	2	2	1
12	Devi	3.3	2.6	2.1	0	1	1	1	2.3	1.6	1.3	1	2	2	2
13	Pandurangan	4.12	2.26	2.34	0	1	1	1	3.12	1.26	1.34	1	2	3	2
14	Karra Issac	2.84	2.21	2.52	0	1	1	1	2.38	1.03	1.35	1	2	3	1
15	Kaliyammal	2.2	2	1.8	0	1	1	1	1.1	1.12	1.26	1	2	3	1
16	Ganesh	3.25	1.6	2	0	1	1	2	1.25	0.97	1.12	1	2	3	2
17	Saroja	2.8	2.2	2.5	0	1	1	1	1.25	1.01	1.1	0	2	3	1
18	Babu	3.4	1.1	1.85	0	1	1	1	2.4	0.97	1.42	1	2	3	1
19	Lakshmi	2.91	1.43	2.9	0	1	1	1	1.91	1.12	1.87	1	2	3	1
20	Raja	3.49	0.97	1.24	0	1	1	2	2.49	0.97	1.11	1	2	3	1
21	Munusamy	2.62	0.96	1.42	0	1	1	1	2.49	0.92	1.12	1	2	3	1
22	Tamilvanan	4.22	2.26	2.34	0	1	1	1	3.22	1.16	1.34	1	2	3	1
23	Mariyaselvam	4.24	2.2	1.2	0	1	1	1	3.24	1.2	1.1	1	2	2	1
24	Balakrishnan	3.7	3.1	2.9	0	1	1	1	2.76	1.2	1.96	1	1	3	1
25	subramani	3.19	0.94	2.24	0	1	1	1	2.82	0.9	1.14	0	2	3	2
26	Chinnadurai	3.45	1.2	2.5	0	`	1	1	2.45	1.2	1.41	1	2	3	1
27	Pandian	3.29	1.09	1.04	0	1	1	2	2.24	1.04	0.9	1	2	3	2
28	Mani	2.24	2	1.8	0	1	1	1	2.22	1.11	1.6	1	1	3	1
29	Raja	3.42	1.12	2.33	0	1	1	1	3.26	1.11	2.12	1	2	3	1
30	Kuppusamy	3.34	1.64	2.02	0	1	1	1	3.25	1.6	2	1	2	2	1

S.NO	NAME	LEFT PAROTID PRE RADIOTHERAPY							LEFT PAROTID POST RADIOTHERAPY						
		L	W	D	M	ET	EG	V	L	W	D	M	ET	EG	V
1	Veerappan	3.92	2.77	1.85	0	1	1	1	2.9	1.25	1.27	1	*1*	3	1
2	Pappammal	3.9	1.2	0.7	0	1	1	1	2.91	1.1	0.7	1	2	3	1
3	Maria john	3.92	2.77	2.4	0	1	1	1	3.58	1.89	1.51	1	2	3	1
4	Sargunan	3.17	1.3	1	0	1	1	1	2.46	1	0.96	1	2	3	1
5	Antony	3.11	0.69	0.62	0	1	1	1	2.87	0.56	0.6	1	2	3	2
6	Uthiramary	3.54	1.09	2.69	0	1	1	1	2.7	0.84	1.97	1	2	3	2
7	Elumalai	3.4	3.3	2.1	0	1	1	1	24.9	2.5	1.1	1	2	3	2
8	Subbaiya	3.8	1.8	1.2	0	1	1	1	2.8	1	1.1	1	2	3	1
9	Saravanan	3.6	1.5	2.1	0	1	1	1	2.65	1.1	1.1	1	2	3	1
10	Rosyammal	3.9	3	2.3	0	1	1	1	3.1	2.26	1.7	1	1	3	1
11	Guruswamy	3.9	1.2	1.1	0	1	1	1	2.9	1.1	1.01	1	2	2	1
12	Devi	3.1	1.6	1.4	0	1	1	1	2.2	0.7	1.01	1	2	2	1
13	Pandurangan	3.6	1.5	2.1	0	1	1	1	2.6	1.4	1.6	1	2	3	3
14	Karra Issac	2.76	2.2	2.32	0	1	1	1	2.49	1.32	1.24	1	2	3	3
15	Kaliyammal	2.3	1.6	1.3	0	1	1	1	1.2	1.24	1.12	1	2	3	3
16	Ganesh	3.27	1.1	1.17	0	1	1	1	2.76	1	1.15	1	2	3	3
17	Saroja	2.7	2.2	2.3	0	1	1	1	2.34	1.67	1.38	1	2	3	3
18	Babu	3.01	1.1	1.2	0	1	1	1	2.01	0.8	1.02	1	1	2	1
19	Lakshmi	3.01	1.1	2.8	0	1	1	1	2.01	1.1	1.8	1	2	3	1
20	Raja	2.8	1.01	0.84	0	1	1	1	1.79	1.01	0.84	1	2	2	1
21	Munusamy	2.2	0.7	2.3	0	1	1	1	1.96	0.7	1.12	1	2	2	1
22	Tamilvanan	4.1	2.2	2.24	0	1	1	1	3.68	2.12	2.12	1	2	2	2
23	Mariyaselvam	4.1	1.6	1.4	0	1	1	1	3.1	1.01	1.1	1	2	3	2
24	Balakrishnan	3.82	1.2	1.2	0	1	1	1	3.62	1.2	1.2	1	2	3	2
25	subramani	3.24	1.2	2.14	0	1	1	1	2.91	1.1	1.97	1	1	3	2
26	Chinnadurai	2.91	1.46	1.27	0	1	1	1	2.84	1.44	1.24	1	2	3	2
27	Pandian	2.43	1.01	1.4	0	1	1	1	2.21	1.01	1.21	1	2	3	2
28	Mani	2.32	1.6	1.3	0	1	1	1	2.12	1.11	1.24	1	2	3	1
29	Raja	3.5	1.1	2.7	0	1	1	1	2.83	0.96	2.34	1	1	3	1
30	Kuppusamy	3.5	1.1	2.2	0	1	1	1	3.27	1.2	2.1	1	2	3	1

S.NO	NAME	RT SUBMANDIBULAR GLAND PRERADIOTHERAPY							RT SUBMANDIBULAR GLAND POST RADIOTHERAPY						
		L	W	D	M	ET	EG	V	L	W	D	M	ET	EG	V
1	Veerappan	3.2	1.63	1.9	0	1	1	1	1.7	0.87	0.96	1	2	1	1
2	Pappammal	3.2	1	1.27	0	1	1	1	2.9	0.9	1.1	0	2	1	1
3	Maria john	3.3	1.8	2.1	0	1	1	1	2.4	1	1.14	0	2	1	1
4	Sargunan	3.1	1.6	1.38	0	1	1	1	2.3	1.56	1.1	0	2	1	1
5	Antony	3	1.09	1.1	0	1	1	1	2.14	1.02	1	0	2	1	2
6	Uthiramary	3.48	1.47	1.2	0	1	1	1	2.69	1.36	0.9	0	2	1	2
7	Elumalai	3.01	1.7	1.56	0	1	1	2	2.4	1.1	0.7	0	2	2	2
8	Subbaiya	3.34	2.28	1.32	0	1	1	1	2.46	1.27	0.9	1	2	2	2
9	Saravanan	3.04	1.44	1.26	0	1	1	1	2.21	1.12	1.1	0	2	2	1
10	Rosyammal	3.2	1.3	1.4	0	1	1	1	2.1	0.87	0.9	0	1	2	1
11	Guruswamy	3.1	1	1.1	0	1	1	1	2.97	0.7	1.1	1	1	2	1
12	Devi	3	1.46	1.39	0	1	1	1	2.12	1.01	1.36	0	1	2	1
13	Pandurangan	3.04	1.4	1.2	0	1	1	1	2.14	1.12	1.1	1	2	3	2
14	Karra Issac	2.45	1.75	2.84	0	1	1	1	1.75	1.24	2.24	1	2	3	1
15	Kaliyammal	2.65	1.4	1.56	0	1	1	1	2.12	1.12	1.46	1	2	3	1
16	Ganesh	3.04	0.97	1.56	0	1	1	1	2.45	0.97	1.46	0	2	3	1
17	Saroja	2.4	1.7	2.8	0	1	1	1	1.42	1.32	2.2	0	2	1	1
18	Babu	3.4	1.1	1.5	0	1	1	1	2.4	1.11	1.12	0	2	1	1
19	Lakshmi	3.2	1.01	3.2	0	1	1	1	2.4	1.01	2.2	1	2	1	1
20	Raja	2.64	1.24	1.43	0	1	1	1	1.64	1.12	1.02	1	2	1	1
21	Munusamy	3.01	1.42	1.74	0	1	1	2	2.56	1.13	1.64	1	2	1	1
22	Tamilvanan	3.3	1.47	1.36	0	1	1	1	2.7	0.9	1.09	0	1	1	1
23	Mariyaselvam	2.9	1.8	2.2	0	1	1	1	2.5	1.64	2.1	0	2	1	1
24	Balakrishnan	3.12	1.2	1.4	0	1	1	1	2.87	1.1	1.26	1	2	2	1
25	subramani	2.98	1.32	1.46	0	1	1	1	2.65	1.4	1.36	0	2	2	1
26	Chinnadurai	3.3	1.4	1.9	0	1	1	1	2.4	1.01	1.14	1	1	2	1
27	Pandian	1.91	0.6	0.8	0	1	1	1	1.67	0.6	0.7	1	2	2	2
28	Mani	2.9	1.8	1.64	0	1	1	1	2.38	1.03	1.35	0	2	3	1
29	Raja	3.2	1.1	3.3	0	1	1	1	2.43	0.85	1.15	1	2	3	1
30	Kuppusamy	2.9	0.8	2.2	0	1	1	2	2.4	0.7	1.97	1	2	1	1

S.NO	NAME	LEFTSUBMANDIBULAR PRE RADIOTHERAPY							LEFT SUBMANDIBULAR POST RADIOTHERAPY						
		L	W	D	M	ET	EG	V	L	W	D	M	ET	EG	V
1	Veerappan	3.4	1.96	1.8	0	1	1	1	2.43	0.85	0.86	1	2	2	1
2	Pappammal	3.48	1.94	2.2	0	1	1	1	2.9	14.4	1.94	0	2	2	1
3	Maria john	3.4	1.7	1.5	0	1	1	1	2.7	0.84	1.21	0	2	2	1
4	Sargunan	2.9	1.29	1.6	0	1	1	1	2.2	0.97	1.2	1	1	3	1
5	Antony	3	1.1	0.8	0	1	1	1	2.74	1	0.67	0	2	3	2
6	Uthiramary	3.41	1.4	1.6	0	1	1	1	2.87	1.1	1.2	0	2	3	2
7	Elumalai	3.2	1.7	1.4	0	1	1	2	2.62	1.22	1.4	1	2	3	2
8	Subbaiya	3.2	1.8	1.6	0	1	1	2	2.6	1.2	1	1	2	3	2
9	Saravanan	3.02	1.46	1.2	0	1	1	1	2.01	1.21	0.97	0	2	2	1
10	Rosyammal	2.95	1.2	1.39	0	1	1	1	2.2	0.7	1.1	0	1	2	1
11	Guruswamy	2.7	1.2	0.9	0	1	1	1	2.6	1.2	0.7	1	1	2	1
12	Devi	2.9	1.3	1.4	0	1	1	1	2.13	0.9	0.8	0	1	3	1
13	Pandurangan	3.01	1.43	1.24	0	1	1	1	2.01	1.02	1.12	0	2	3	1
14	Karra Issac	2.62	1.22	5	0	1	1	1	2.21	1.12	1.42	0	2	3	1
15	Kaliyammal	2.9	1.67	1.58	0	1	1	1	2.4	1.1	1.28	0	2	3	2
16	Ganesh	2.9	0.9	2.1	0	1	1	1	2.12	1.01	1.36	1	2	3	1
17	Saroja	2.69	1.2	1.6	0	1	1	1	2.19	1.1	1.2	0	1	3	1
18	Babu	3.4	1.4	1.8	0	1	1	1	2.4	1.1	1.2	0	1	1	1
19	Lakshmi	3.1	1.1	2.8	0	1	1	1	2.8	0.97	1.4	1	2	1	1
20	Raja	3	0.9	1.1	0	1	1	1	2.6	0.9	1.1	0	2	3	2
21	Munusamy	2.4	1.1	1.5	0	1	1	2	2.2	0.7	1.1	0	2	1	1
22	Tamilvanan	3.2	1.42	1.4	0	1	1	1	2.86	1.21	1.2	0	2	3	2
23	Mariyaselvam	3.1	1.9	1.56	0	1	1	1	2.8	1.4	1.34	0	1	3	1
24	Balakrishnan	3.01	1.4	1.34	0	1	1	1	2.97	1.3	1.24	1	1	3	1
25	subramani	2.96	1.4	1.42	0	1	1	1	2.65	1.32	1.36	0	2	3	1
26	Chinnadurai	3.1	1.2	1.2	0	1	1	1	2.46	1.01	1.24	1	2	3	1
27	Pandian	1.91	0.9	0.82	0	1	1	1	1.64	0.7	0.7	1	2	3	1
28	Mani	3.1	1.9	1.56	0	1	1	1	2.97	1.3	1.25	1	2	3	2
29	Raja	3.2	1.1	2.4	0	1	1	1	2.6	1.03	1.4	0	2	3	1
30	Kuppusamy	2.7	0.9	1.9	0	1	1	1	2.4	0.7	1.25	0	1	3	1

S.NO	NAME	SALIVARY BIOCHEMICAL CHANGES PRE RADIOTHERAPY AND POST RADIOTHERAPY											
		SODIUM		POTTASIUM		CALCIUM		PH		AMYLASE		TOTAL PROTEIN	
		PRE RT	POST	PRE RT	POST	PRE RT	POST	PRE RT	POST	PRERT	POST	PRERT	POST
1	Veerappan												
2	Pappammal	14.8	36.6	16.71	16.01	5.2	6.4	7	5	146.2	16.3	1.49	1.81
3	Maria john	20.2	51.2	18.51	17.24	4.1	5.2	6	6	260.7	21.1	1.62	1.88
4	Sargunan	19.8	46.6	20.06	18.32	3.74	3.94	6	5	246.4	18.9	1.83	2.41
5	Antony	22.12	42.2	24.4	22.67	3.31	4.21	6	5	116.2	10.6	1.37	1.77
6	Uthiramary	14.6	17.8	29.5	28.1	2.9	4.44	7	5	189.5	17.4	1.29	1.57
7	Elumalai	18.7	38.6	16.36	14.3	3.1	5.7	6	6	168.4	15.4	1.53	1.81
8	Subbaiya	19.7	27.2	24.17	23.67	1.8	2.4	7	5	374.6	21.4	1.94	2.24
9	Saravanan	18.6	44.3	18.42	16.2	3.2	5.2	6	5	377.4	22.6	1.49	1.79
10	Rosyammal	20.1	57.2	15.3	13.7	2.9	3.8	6	5	484.7	26.4	1.41	1.87
11	Guruswamy	14.3	26.1	17.8	16.1	3.6	4.2	7	6	680.4	20.54	1.94	2.34
12	Devi	16.8	31.3	12.64	10.72	4.2	6.4	7	5	394.8	16.87	1.21	1.56
13	Pandurangan	18.8	44.2	17.3	16.21	3.3	4.2	7	5	489.4	22.3	1.47	1.79
14	Karra Issac	21.2	52.4	20.4	18.6	3.8	5.6	6	5	168.9	10.7	1.97	2.24
15	Kaliyammal	14.8	48.4	21.44	20.24	5.1	6.2	6	5	624.4	21.4	2.53	2.61
16	Ganesh	10.7	32.6	15.3	13.12	4.3	6.2	7	6	117.1	8.03	1.78	1.99
17	Saroja	32.5	68.7	15.6	13.7	4.8	6.1	7	6	784.6	36.7	1.86	2.14
18	Babu	17.4	47.3	14.43	13.42	2.9	6.2	6	5	289.3	18.41	1.31	1.71
19	Lakshmi	19.9	43.1	20.2	18.1	2.8	3.8	6	5	270.2	19.7	1.61	1.81
20	Raja	36.4	69.4	11.62	10.62	1.9	2.8	6	5	1109	487.12	1.82	2.14
21	Munusamy	21.8	57.6	17.2	16.12	3.2	3.2	7	5	1095	346.41	1.27	1.57
22	Tamilvanan	14.7	38.9	16.4	15.01	4.7	5.2	6	5	376.4	28.21	1.37	1.62
23	Mariyaselvam	36.1	65.4	11.2	9.11	5.1	6.2	7	6	216.4	17.12	1.17	1.36
24	Balakrishnan	16.6	34.2	14.2	13.15	3.7	4.2	7	5	381.6	21.47	1.17	1.53
25	subramani	14.9	31.1	16.1	14.87	4.12	5.2	7	5	328.5	26.72	1.18	1.34
26	Chinnadurai	22.3	41.5	12.3	11.26	4.4	5.1	7	5	296.4	17.41	1.13	1.62
27	Pandian	20.7	40.8	17.3	15.7	3.8	4.2	7	5	424.3	24.21	1.27	1.61
28	Mani	21.2	46.4	32.2	31.2	2.8	3.7	7	6	346.4	23.42	1.81	2.09
29	Raja	14.8	49.3	25.7	25	2.91	3.9	6	6	146.4	13.17	1.13	1.47
30	Kuppusamy	12.7	38.6	16.23	14.14	3.2	4.6	6	5	129.1	17.23	1.31	1.74